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(Continued)

REACTIONS TO ANTIPNEUMOCOCCAL RABBIT SERUM*†

II. FAILURE TO ADSORB SENSITIZING ANTIBODY BY KIESELGUHR, FULLERS' EARTH, BERKEFELD FILTRATIONS, AND ALUMINUM HYDROXIDE

OSCAR SWINEFORD, JR., M.D., UNIVERSITY, VA.

ANAPHYLACTIC reactions to antipneumococcal rabbit serum are thought to be due to reversed passive anaphylaxis when tests for sensitivity to rabbit serum are negative.[1] Separation of the anaphylactic from the therapeutic antibody would offer a means of preventing these reactions. Heat does not separate these antibodies in refined antipneumococcal rabbit serum.[1] This is in contrast to the ready separation, by Loveless,[2] of the human thermostable antibody from reagin by 56° C. in five hours or by 60° C. in one hour.

Foshay[3] described an erythematous-edematous (E-E) reaction, grossly indistinguishable from the conventional positive allergic cutaneous reaction, produced by injecting specific antiserum into the skin of an infected person. He stated that the factor responsible for this highly specific reaction could be adsorbed by fullers' earth, kieselguhr, five successive Berkefeld filtrations, aluminum hydroxide, or aluminum silicate. The adsorption was complete from horse and goat antisera specific for streptococci, staphylococci, *Bacillus tularense, Brucella,* gonococci, lymphogranuloma virus, and tubercle bacilli. He did not mention the E-E reaction nor the adsorption of the E-E reaction factor in pneumonia. The adsorption of the E-E reaction factor did not reduce the agglutinins or the opsonin titers. It did reduce the precipitin titer of the antiserum against tularense-specific polysaccharide.

An attempt was made to separate the sensitizing from the therapeutic antibody in antipneumococcal rabbit serum by adsorption with these materials. This was done on the assumption that the E-E reaction is simply a manifestation of local reversed passive anaphylaxis. This obviously tentative assumption was suggested by the fact that each is produced by the injection of antiserum into tissues presumed to contain specific antigen.

*From the Allergy Clinic, Department of Internal Medicine, University of Virginia Medical School, Charlottesville, Va.

†This is one of several studies made possible by a grant plus generous supplies of antipneumococcal rabbit serum from Wyeth Incorporated, Philadelphia, Pa.

Experiment 1A.—Ten milliliters of Type II antipneumococcal rabbit serum were sucked gently through 7 Gm. of sterile fullers' earth in a small Seitz filter. One and one-half milliliters of filtrate were injected intra-abdominally into each of two guinea pigs. Two days later 1 ml. (1 mg.), of Type II pneumococcal polysaccharide, administered intravenously, caused the prompt typical anaphylactic death of each animal.

Foshay found that 7 ml. of fullers' earth would adsorb the E-E reaction factor from 20 ml. of antiserum.

Experiment 1B.—Fullers' earth was added to 5 ml. of Type II antipneumococcal antiserum until all but about 2 ml. seemed to be adsorbed. This mixture was emulsified by inverting frequently for four days. Between mixings it was kept in the icebox. After centrifuging, 1 ml. of the supernate was injected intra-abdominally into each of two guinea pigs.

Two days later, 1 ml. of Type II polysaccharide, 0.2 mg. per milliliter, was injected into the jugular vein of one of the animals, and 1.5 ml. were injected into the other. Both animals died promptly in typical anaphylactic shock.

Experiment 2.—Ten milliliters of Type II antipneumoococcal rabbit serum diluted with equal parts of normal saline were sucked gently through five Berkefeld filters. One and one-half milliliters of the filtrate were injected intra-abdominally into each of two guinea pigs. Two days later 1 ml. (1.0 mg.) of Type II pneumococcal polysaccharide, administered intravenously, caused the prompt typical anaphylactic death of each animal.

Experiment 3.—Ten milliliters of Type I antipneumococcal rabbit serum were mixed thoroughly with an equal volume of kieselguhr. Mixing was repeated several times daily for three days. One and one-half milliliters of the supernate were injected intra-abdominally into each of three guinea pigs. Two days later, 1 ml. (1 mg.) of Type II pneumococcal polysaccharide, administered intravenously, caused no reaction. One milliliter (1 mg.) of Type I polysaccharide injected a few minutes later caused the prompt anaphylactic death of each animal.

Experiment 4.—Type II serum was treated as in Experiment 1B.; aluminum hydroxide was used instead of fullers' earth. Each of two guinea pigs was sensitized by the intra-abdominal injection of 1 ml. of this supernate. Intravenous injections of 1.25 ml. of polysaccharide solution, 0.2 mg. per milliliter, were followed in both animals by prompt fatal anaphylactic shock.

SUMMARY

1. The anaphylactic antibody was not absorbed demonstrably from antipneumococcal rabbit serum by fullers' earth, kieselguhr, multiple Berkefeld filtration, or aluminum hydroxide. This is in contrast with the reported[3] adsorption of the E-E reaction factor from a variety of antisera by these substances.

2. It is of some importance that the possible identity of the E-E reaction and local reversed passive anaphylaxis be proved or disproved. Foshay[3] claims

that anaphylaxis from antisera (other than antipneumococcal) is not predisposed to by the presence of the E-E reaction. There is evidence[4] to suggest that an excess of specific polysaccharide does predispose to anaphylaxis from antipneumococcal rabbit serum.

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REACTIONS TO ANTIPNEUMOCOCCAL RABBIT SERUM*†‡

III. Effects of Varying Amounts of Pneumococcal Polysaccharide on Reversed Passive Anaphylaxis in Guinea Pigs

IV. A Simple Roughly Quantitative Method of Measuring Circulating Polysaccharide

H. Rowland Pearsall, M.D., Stanton L. Eversole, M.D., and Oscar Swineford, Jr., M.D., University, Va.

PROMPT anaphylactic reactions to therapeutic injections of antipneumococcal rabbit serum are common. Conventional anaphylaxis is the accepted mechanism for these reactions when cutaneous, conjunctival, and intravenous tests for sensitivity are positive. Reversed passive anaphylaxis is believed to mediate the reactions when tests for sensitivity to rabbit serum are negative.[1] Tests for sensitivity were negative in nearly 80 per cent of recorded reactions to antipneumococcal serum.[2]

It is desirable to reduce this number of reversed passive anaphylactic reactions which occur when tests for sensitivity to rabbit serum are negative. Measurable amounts of circulating polysaccharide are found in some patients with pneumonia.[3-5] The patient who has circulating polysaccharide has a poor prognosis and thereby becomes a candidate for antiserum.[3] It was logical, therefore, to study the role of circulating polysaccharide in the production of reversed passive anaphylaxis.

This is the report (1) of the effects of varying amounts of pneumococcal polysaccharide on reversed passive anaphylactic reactions in guinea pigs, (2) of a simple roughly quantitative method for measuring circulating polysaccharide, and (3) some tentative applications of (1) and (2) to the problem of serum therapy in pneumonia and to the theories of the role of antigen in reversed anaphylaxis.

METHODS

Stock Types I and II polysaccharide solutions, 10 mg. per milliliter, were used as antigen. Several batches of Type I and Type II antipneumococcal rabbit serum were used.

All injections were made into the jugular veins of guinea pigs. The average time for each injection was fifteen to thirty seconds. The work was facilitated by a bivalved plaster guinea pig holder.[6]

*From the Allergy Clinic, Department of Internal Medicine, University of Virginia Medical School, Charlottesville, Va.

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Each batch of serum was tested for primary toxicity by intravenous injections of 2 to 3 ml. of undiluted serum into at least two pigs. These and the animals which did not react in Experiments 1 and 2 served as negative controls.

The interval between sensitizing injections of polysaccharide and administration of the shocking doses of serum was sixty to ninety minutes. Previous experiments[1] had indicated that this interval approximated the optimum.

In Experiment 1, 2 ml. (10,000 units per milliliter) of Type I antiserum were used as the shocking dose. In Experiment 2, 2 ml. (2,000 units per milliliter) of Type II antiserum were used. The volume of serum was the same, but the unit-strength was different in the two experiments.

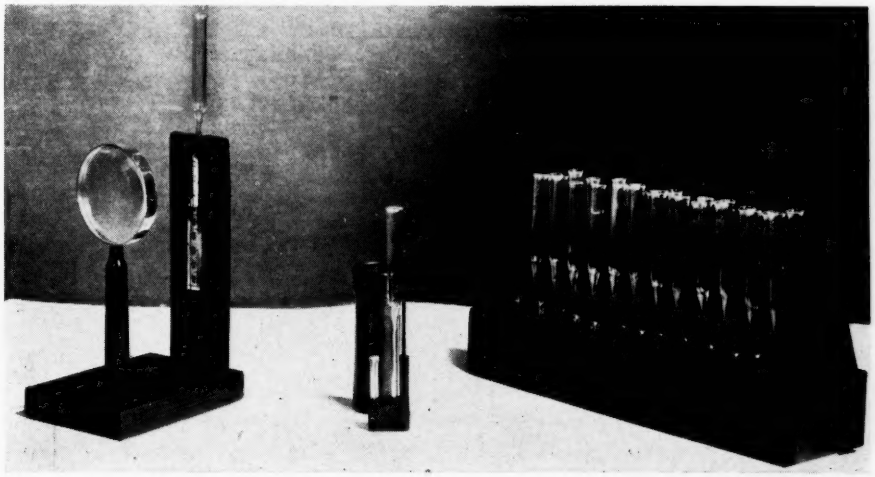

Fig. 1.

The data shown in Table III were obtained by precipitin tests on blood removed from the jugular veins of guinea pigs of approximately the same weight. The serum of this blood was titrated for circulating polysaccharide in a capillary "J" tube[7] as follows:

One-tenth of one milliliter of guinea pig serum was added to 0.5 ml. of antipneumococcal serum in the "J" tube. This was then agitated in a mechanical shaker for five minutes, incubated at 37° C. for one hour, and kept in the icebox overnight. Two milliliters of saline introduced through the filling bulb as a diluent greatly reduced the tendency to clog the entrance to the capillary portion of the "J" tube when there was a large amount of precipitate. The mixtures were then centrifuged at 2,000 r.p.m. for forty-five minutes to obtain maximum packing. The volumes of precipitates were calculated from the height in the capillary tubes, the diameters of which had been calibrated individually.

Fig. 1 shows the special holders for the "J" tubes to insure long-axis position in the centrifuge cups, protection in the shaker, and ease of handling. The apparatus for measuring the height of the precipitate in the tubes is also shown in Fig. 1.

There are several sources of error, not yet studied, which make the results of this method of measuring precipitates only roughly quantitative. Numerous duplicate determinations, not included here, have shown that the method is accurate enough for the purposes of this report.

The precipitin tests in Experiment 4 differed from those in Experiment 3 in that the "J" tubes were centrifuged for only fifteen minutes immediately after shaking for five minutes and incubation at 37° C. for one hour. It is obvious that serum, plasma, or other solutions should be freed of cells and debris by centrifugation before these tests are done. Controls of serum and saline and of polysaccharide and nonspecific serum were all negative.

EXPERIMENTAL DATA

In Experiment 1 (Table I) the sensitizing dose of Type I polysaccharide was varied. The shocking dose of Type I antiserum was constant. The interval between sensitizing and shocking doses was varied by only a few minutes. The tabulated data show that no reaction occurred when the sensitizing dose of polysaccharide was 0.02 mg. or less. There were some definite but no severe reactions when the sensitizing dose was 0.1 milligram. In sharp contrast is the high percentage of typical anaphylactic deaths when 0.5 mg. or more of polysaccharide was used. Three different effective batches of Type I antiserum were used.

TABLE I. REVERSED PASSIVE ANAPHYLAXIS; EFFECT OF VARYING SENSITIZING DOSE OF TYPE I POLYSACCHARIDE

(Interval, sixty to ninety minutes; shocking dose of Type I antiserum, 2 ml.)

SENSITIZING DOSE TYPE I POLYSACCHARIDE (MG.)	REACTIONS							
0.01	0	0	0	0	0	0	0	
0.02	0	0	0	0	0			
0.1	+	++	0	+	+	0	0	
0.5	AD	AD	AD	AD	AD	++	AD	+
1.0	AD	AD	AD	AD	AD	++	AD	AD
1.5	AD	AD	AD	AD	AD	AD		
2.0	AD	AD	++	AD				
3.0	AD	AD						
4.0	AD							

+, Slight reaction; prolonged expiration, ruffled hair, obvious dyspnea.

++, Moderate reaction; marked expiratory dyspnea, obviously sick.

AD, Typical anaphylactic death; autopsy showed pale ballooned lungs with scattered hemorrhagic areas.

The post-mortem findings of large, pale, ballooned lungs with hemorrhagic foci were typical of reversed passive anaphylaxis as described by Dean, Williamson, and Taylor[8] and others.

Experiment 2 (Table II) differed from Experiment 1 chiefly in the use of Type II polysaccharide and antiserum as sensitizing antigen and shocking antiserum. The data show similar qualitative results in that there were no reactions when the sensitizing dose was below a certain level (0.005 mg.); whereas there was a high percentage of reactions when the sensitizing dose was above 1.5 milligrams. Likewise, one of the three batches of serum used seemed less anaphylactogenic than the other. There were quantitative differences, however, between the data in the two experiments. The minimum sensitizing dose

TABLE II. REVERSED PASSIVE ANAPHYLAXIS; EFFECT OF VARYING SENSITIZING DOSE OF TYPE II POLYSACCHARIDE

(Interval, sixty to ninety minutes; shocking dose of Type II antiserum, 2 ml.)

SENSITIZING DOSE TYPE II POLYSACCHARIDE (MG.)	REACTIONS												
0.001	0	0	0	0	0								
0.0025	0	0	0	0	0								
0.005	0	+	0	0	+								
0.01	0	0	AD	++	0	0	0						
0.02	AD	0	0	AD	AD	0	AD	AD	0	0	0	0	0
0.1	0	0	0	0	++	0	0	0	0	0			
0.5	0	++	0	0	0	0	0	0					
1.0	0	AD	0	AD	0	0	0	0					
1.5	+	++	++	AD	+								
2.0	AD	++	++	++	AD								
3.0	AD	AD	++	++	++								
4.0	AD	AD	++	++	++								

+, Slight reaction; prolonged expiration, ruffled hair, obvious dyspnea.

++, Moderate reaction; marked expiratory dyspnea, obviously sick.

AD, Typical anaphylactic death; autopsy showed pale, ballooned lungs with scattered hemorrhagic areas.

of polysaccharide was lower (0.01 mg.) and the lowest uniformly sensitizing dose was higher (1.5 mg.) than they were in Experiment 1. The chief difference, however, was the high incidence of anaphylactic deaths in the groups given 0.01 and 0.02 mg. and the few reactions in the groups given more and less polysaccharide.

Little effort was made to explain these quantitative differences.

Experiment 3 (Table III) shows (1) that polysaccharide injected intravenously persists in the circulating blood of guinea pigs for at least one hour in measurable quantities roughly proportional to the amount injected, and (2) that the reversed passive anaphylactic reactions in Experiments 1 and 2 occurred in the presence of increasing excesses of circulating polysaccharide.

TABLE III. MEASUREMENT OF CIRCULATING POLYSACCHARIDE IN GUINEA PIGS ONE HOUR AFTER INTRAVENOUS INJECTIONS OF DIFFERENT AMOUNTS*

AMOUNT TYPE I POLYSACCHARIDE INTRAVENOUSLY (MG.)	SERUM DRAWN 1 HR LATER (ML.)	TYPE I ANTISERUM (ML.)	VOLUME OF PRECIPITATE† (C.MM.)
0.1	0.1	0.5	1.5‡
0.5	0.1	0.5	2.8
1.0	0.1	0.5	3.9
1.5	0.1	0.5	5.8
2.0	0.1	0.5	8.6

*Measured by precipitation in capillary "J" tubes.

†See method for details.

‡Average for two pigs.

Experiment 4A (Table IVA) showed that 0.0005 mg. of pneumococcal polysaccharide in saline is readily detected in the capillary "J" tube after shaking for five minutes, incubation for only one hour, and centrifuging for fifteen minutes. Polysaccharide diluted with plasma gave similar results.

Experiment 4B (Table IVB) showed that small amounts of polysaccharide injected intravenously can be detected in the plasma of a patient ten minutes later.

TABLE IVA. DETECTION OF TYPE I POLYSACCHARIDE IN SALINE*

AMOUNT POLYSACCHARIDE IN 0.5 ML. SALINE (MG.)	PRECIPITATE IN "J" TUBE (C.MM.)
0.01	11.3
0.001	0.678
0.0005	0.373
0.0001	Trace

*See method for details. Centrifugation immediately after incubation for one hour at 37° C. and shaking for five minutes.

TABLE IVB. DETECTION OF TYPE I POLYSACCHARIDE IN SERUM OF PATIENT*

AMOUNT PATIENT'S SERUM (ML.)	ESTIMATED AMOUNT POLYSACCHARIDE (MG.)	PRECIPITATE IN "J" TUBE (C.MM.)
0.1	0.00033	0.383
0.5	0.00165	1.560
1.0	0.0033	4.759
2.0	0.0066	10.584

*Ten milligrams of Type I polysaccharide were injected into patient with estimated plasma volume of 3,000 milliliters. Ten minutes were allowed for mixing before blood sample was drawn.

Longer incubation and centrifuging did not materially effect the sensitivity of the test as a method for demonstrating minute quantities of polysaccharide.

Experiments 4A and 4B were repeated with Bullowa's method,[3, 9] using 7-mm. precipitin tubes instead of the capillary "J" tubes. Differences in titer, which favored the "J" tube, were not striking. Definite advantages of the "J" tube are (1) the ease with which the white opalescent specific precipitate can be differentiated in it from traces of nonspecific detritus, and (2) the fact that quantitative measurements of the amount of precipitate can be made.

DISCUSSION

The incidence of reversed passive anaphylaxis was highest in those guinea pigs with an appreciable excess of circulating antigen. This is in direct contrast to the belief of Van den Ende[10] that an excess of circulating antigen would inhibit the reaction. By analogy, therapeutic serum would be more likely to cause reversed passive anaphylaxis in patients with circulating polysaccharide than in those without it. Yet these are the cases in which serum is strongly recommended.[3] It would seem desirable, therefore, to test the plasma or serum of pneumonia patients for circulating polysaccharide before giving antiserum. The capillary "J" tube permits reasonably accurate quantitative polysaccharide determinations. Ordinary precipitin tubes can be used for qualitative determinations in the absence of "J" tubes. If definite amounts of circulating polysaccharide are found it would seem reasonable to advise that therapeutic antiserum be given slowly and in small amounts initially. Obviously the soundness of this advice needs clinical confirmation.

The possibility that excess circulating polysaccharide may be responsible for some of the positive intracutaneous reactions to antipneumococcal serum has been discussed elsewhere.[1, 11] Again by analogy, the likelihood of reversed passive anaphylactic reactions to antiserum would be greater if positive allergic

intracutaneous reactions were obtained with the specific antiserum but not with normal serum. This has not yet been applied clinically.

These observations do not by any means solve the problems of the administration of antiserum to pneumonia patients. The lives of many extremely ill patients have been saved by the use of antiserum, without untoward reactions. In guinea pigs and in man the incidence of severe reactions to antiserum is influenced by other factors about which little is known.

The high incidence of reversed passive anaphylaxis in the presence of a considerable excess of circulating antigen is at variance with the theory of Kellett,[12] Van den Ende,[10] and others that reversed passive anaphylaxis is mediated by antigen fixed to the tissue cells. This theory of fixed antigen is also difficult to reconcile with the reversed passive anaphylactic reactions produced by Zinsser and Enders[13] by injecting antibody only a few minutes after antigen, or with the conventional passive anaphylactic reactions produced by Dean, Williamson, and Taylor[8] by injecting antigen immediately after antiserum.

The effects on reversed passive anaphylaxis of varying the shocking dose of antiserum and the speed of administration of the shocking dose are being studied.

CONCLUSIONS

1. Reversed passive anaphylaxis can be produced in guinea pigs, almost at will, by injecting an excess of pneumococcus polysaccharide about one hour before injecting type-specific antipneumococcal rabibt serum.

2. One current criterion for the clinical use of antiserum in pneumonia is analogous to one condition most conducive to reversed anaphylaxis in guinea pigs, namely, an excess of circulating polysaccharide.

3. A simple quick roughly quantitative method for measuring circulating polysaccharide is described.

4. Evidence is presented which is at variance with the theory that reversed passive anaphylaxis is mediated by fixed antigen.

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LEUCOCYTE FRAGILITY IN TRANSITORY LEUCOPENIA*

THEODORE L. SQUIER, M.D., MILWAUKEE, WIS.

TRANSITORY leucopenia is a manifestation as important and as characteristic of allergic reactions as is eosinophilia. In fact, von Pirquet and Schick[1] stated in their classic description of serum disease that in certain instances, leucopenia might be the only recognizable manifestation of the condition. Redistribution of leucocytes undoubtedly is the major cause of the rapid fall in white cells which occurs in allergic shock. During an acute anaphylactic reaction, white cells presumably are shunted into the lung and possibly into the spleen and other organs. Experimentally, Webb[2] showed that blood taken from the pulmonary vein of a dog during anaphylactic shock contained appreciably fewer leucocytes than did that from the pulmonary artery. Sections of such lungs showed enormous numbers of leucocytes crowding the capillaries and adherent to the vessel walls; this confirmed his inference that there was leucocyte loss in the pulmonary area. Similar adherence of leucocytes to peripheral vessel walls was demonstrated more recently by Abel and Schenck.[3] Using an ingenious moat, they observed the circulation in a rabbit's ear under the microscope during anaphylactic shock. In the first phase of shock arteriolar contraction with obliteration of lumen was noted. This was followed by increased adherence of leucocytes to the blood vascular endothelium and, finally, by emigration of leucocytes through the walls of capillaries and venules.

Although redistribution of leucocytes appears to be of major importance, it is probable that increased destruction of leucocytes likewise occurs during anaphylactic shock. Webb[2] attempted to demonstrate such leucocyte destruction both in vitro and in vivo. Horse serum was added in vitro to citrated blood taken from a dog previously sensitized with horse serum. White cell counts made before and after the addition of horse serum remained level. In vivo experiments likewise failed to show leucocyte destruction.

Leucocytolysis is much more difficult to demonstrate than is erythrocytolysis, since there is no pigment released from the white cell to act as an index of destruction as in the lysis of red blood cells. However, by making comparative white counts with two diluting fluids in which the leucocytes disintegrate at different speeds, it is possible to estimate the approximate degree of leucocyte fragility. In the usual acetic acid diluent used for white counts leucocytes are comparatively stable, whereas in acetone-eosin diluting fluid such as originally described by Friedman, they are relatively fragile and disintegrate rather rapidly. Squier and Madison[4] reported the use of this acetone eosin diluting fluid in following the blood response after food ingestion. They made simultaneous leucocyte and so-called eosinophile counts and found an increase

*Read before the Second Annual Meeting of the American Academy of Allergy, Chicago, Ill., Dec. 10, 1945.

in the number of eosin-staining leucocytes quite regularly associated with leucopenic blood responses. Subsequent observations demonstrated that many of these pink-staining cells were not true eosinophiles and were referred to in later discussions simply as eosin-staining cells. It was suspected that the increased ability of some leucocytes to take eosin stain might be significant and might be the result of increased permeability of the cell membrane. Accordingly, a series of white counts were made in which standard acetic and acetone-eosin diluting fluids were used for simultaneous counts to establish data for the expression of normal relative white cell fragility. The procedure used may be considered roughly comparable with that for determination of relative red cell fragility in dilutions of hypotonic saline. It differs in that the relative fragility of white cells is estimated by comparing the number of disintegrated leucocytes in the acetone diluting fluid with a simultaneously determined standard white count.

In the fasting state, it was found that the number of leucocytes destroyed in the acetone diluent increased in direct proportion with the rise in the leucocyte count. The percentages of leucocytes destroyed under the conditions described and termed, for convenience, relative fragility indices are shown in the table for fasting white count levels between 5,000 and 12,000.

TABLE I

W.B.C.*	MEAN RELATIVE FRAGILITY INDEX	STANDARD DEVIATION ϵ	MAXIMUM NORMAL FRAGILITY INDEX (MEAN + 2 ϵ)
5,000- 5,499	0.08	0.067	0.21
5,500- 5,999	0.11	0.065	0.24
6,000- 6,499	0.17	0.051	0.27
6,500- 6,999	0.22	0.062	0.34
7,000- 7,499	0.27	0.068	0.40
7,500- 7,999	0.27	0.080	0.43
8,000- 8,499	0.32	0.058	0.44
8,500- 8,999	0.34	0.066	0.48
9,000- 9,499	0.36	0.075	0.51
9,499- 9,999	0.41	0.066	0.54
10,000-10,999	0.40	0.084	0.57
11,000-11,999	0.46	0.059	0.58

*All counts were made in the fasting state. There were twenty-five patients in each group.

Simultaneous acetic and acetone white cell counts were made in the fasting state and forty-five minutes after the ingestion of single foods. Relative fragility indices were determined before and after ingestion in 150 instances in which transitory postingestion leucopenia occurred and in 150 instances in which the postingestion white cell count was increased. The fragility indices so determined were plotted in relation to the corresponding white cell counts as determined in acetic acid diluent. In 150 tests in which postingestion leucopenia occurred, the white cell fragility was significantly increased over that determined for leucocytes in the fasting state. In 150 tests in which a postingestion increase in the white cell count occurred, the leucocytes were either less fragile than they were in the fasting state or the fragility index fell within the normal range. These results are shown graphically in Fig. 1.

The increased white cell fragility observed in transitory leucopenia might result from several mechanisms acting singly or in combination. (1) *Injury* to the cell membrane resulting from antigen-antibody union might cause increased fragility. (2) *Injury* to the cell membrane might result from chemical action or physical trauma and cause increased fragility. (3) *Changes* in the number of circulating leucocytes could increase the relative numbers of older and therefore more fragile cells. (4) *A change* in the relative number of polymorphonuclear or other white cell types could alter the relative leucocyte fragility.

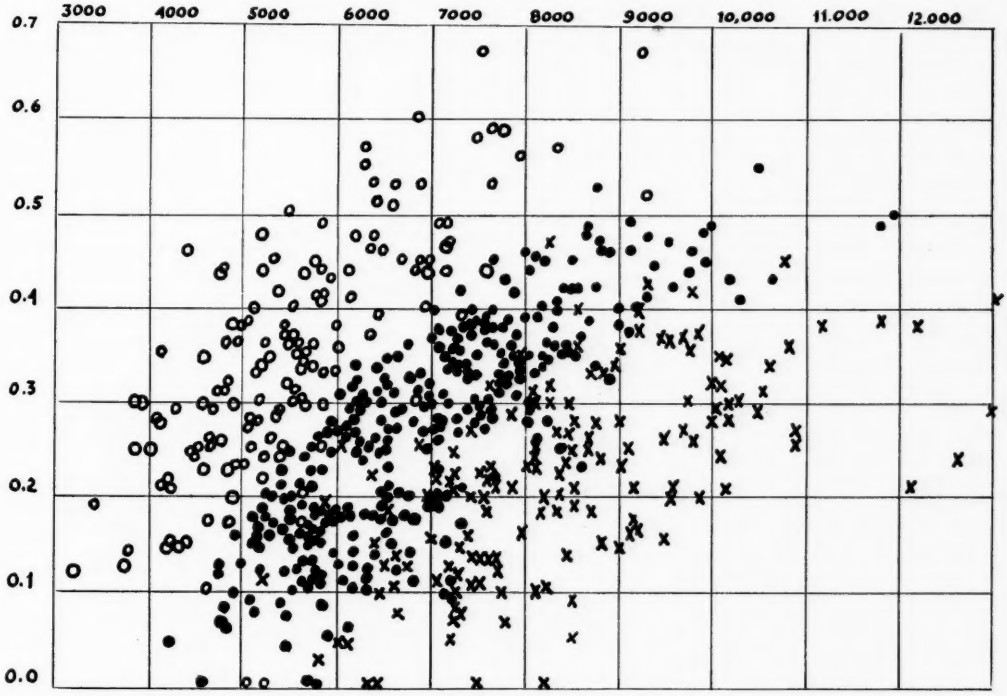

Fig. 1.—Relative fragility indices determined in the fasting state (solid circles), and forty-five minutes after the ingestion of single foods. Leucocyte fragility indices are plotted as ordinates with the corresponding leucocyte counts as abscissas. Postingestion indices in leucopenic responses are shown as open circles; those in which postingestion leucocyte increase occurred are shown as crosses.

The relative proportions of polymorphonuclear and other white cells were studied in two series in which differential counts were made before and after food ingestion. The first group included 28 instances in which transitory leucopenia and an associated increase in white cell fragility were present (Table II). In a second group were 25 instances in which a postingestion leucocyte increase occurred accompanied by unchanged or diminished fragility of the leucocytes (Table III). These data are summarized in Table IV.

During postingestion leucopenia, a fairly uniform reduction was observed in the absolute numbers of all white cell types. Therefore, one is justified in assuming with reasonable probability that the increased leucocyte fragility which was seen is not due to a change in the relative number of polymorphonu-

TABLE II. DIFFERENTIAL COUNTS IN TWENTY-EIGHT INSTANCES IN WHICH THERE WERE TRANSITORY POSTINGESTION LEUCOPENIA AND AN ASSOCIATED INCREASE IN LEUCOCYTE FRAGILITY

ACETIC W.B.C.	ACETONE W.B.C.	FRAGILITY INDEX	NEUTROPHILES I	II	III	IV	V	TOTAL NEUTROPHILES	EOSINOPHILES	BASOPHILES	MONONUCLEARS	SMALL LYMPHOCYTES	LARGE LYMPHOCYTES
Fasting Counts													
7.50	4.40	0.41	3.5	29.5	27.5	3.5	1.0	65.0	4.0	0.0	0.5	28.0	2.5
6.75	5.05	0.25	1.0	18.0	24.0	6.5	0.5	50.0	10.0	0.5	2.5	34.0	3.0
6.25	4.80	0.23	1.0	20.5	26.0	11.5	1.5	60.5	6.5	0.0	2.0	26.0	5.0
6.50	5.05	0.22	1.0	39.0	27.5	4.5	0.0	72.0	1.0	0.0	0.0	25.0	2.0
7.10	4.35	0.38	1.0	20.5	19.5	4.5	0.0	45.5	7.0	0.0	2.0	43.0	2.5
6.90	4.50	0.34	1.0	20.0	17.0	4.5	0.5	43.0	6.5	0.0	0.5	46.5	3.5
9.60	5.45	0.43	1.0	30.5	26.5	7.0	2.0	67.0	0.0	0.0	1.0	29.5	2.5
6.35	5.00	0.21	1.0	23.0	25.0	4.0	0.0	53.0	6.5	0.5	3.5	33.0	3.5
5.30	4.30	0.18	2.5	18.0	18.0	6.5	0.0	45.0	4.0	0.0	2.0	45.5	3.5
6.65	4.85	0.26	0.5	20.5	10.0	5.0	0.5	36.5	3.5	0.0	0.0	57.5	2.5
5.20	4.70	0.09	2.5	28.5	15.5	7.0	0.0	53.5	4.5	0.0	2.5	36.5	3.0
4.90	4.70	0.04	1.5	29.5	15.5	4.5	0.0	51.0	4.5	0.0	1.5	38.5	4.5
5.70	4.20	0.26	0.0	37.0	16.5	4.5	0.0	58.0	14.5	0.0	1.0	26.0	0.5
6.85	4.95	0.27	0.0	20.0	15.5	4.0	1.0	40.5	2.0	0.0	0.5	56.0	1.0
6.35	4.70	0.25	1.0	44.5	15.5	1.0	0.0	62.0	1.5	0.0	0.5	33.0	3.0
5.25	5.00	0.04	1.0	25.0	15.5	4.5	0.0	46.0	9.0	0.0	1.5	42.0	1.5
7.15	5.05	0.29	2.5	33.5	17.0	3.5	0.0	56.5	8.5	0.0	2.0	31.5	1.5
5.50	5.25	0.04	1.0	36.5	19.0	2.5	0.5	59.5	3.5	0.0	2.5	31.5	3.0
7.70	4.25	0.44	2.0	36.0	12.5	2.0	0.0	52.5	20.0	0.0	2.5	22.5	2.5
7.30	5.30	0.27	2.5	38.0	13.5	1.5	0.0	55.5	4.5	0.0	1.5	33.0	5.5
7.30	4.70	0.36	1.5	40.0	19.0	2.0	0.0	62.5	1.5	0.0	2.0	30.0	4.0
6.90	5.70	0.17	1.5	33.5	11.0	2.5	0.0	48.5	10.0	0.0	2.5	36.5	2.5
5.25	4.00	0.24	2.0	40.5	16.0	2.5	0.0	61.0	8.0	0.5	0.5	25.5	4.5
7.50	5.05	0.33	2.0	42.5	11.5	1.5	0.5	58.0	7.0	0.0	4.0	27.5	3.5
5.85	5.50	0.06	0.5	26.0	18.5	2.0	0.0	47.0	3.0	0.0	1.5	44.5	4.0
6.90	4.55	0.34	0.5	34.5	18.0	2.5	0.0	55.5	5.0	0.0	3.5	32.5	3.5
5.70	4.35	0.24	1.0	27.0	23.0	9.0	0.0	60.0	3.0	0.0	3.0	33.5	1.5
6.45	4.70	0.27	2.0	46.5	13.5	2.5	0.5	65.0	3.5	0.0	1.0	27.5	3.0
6.50	5.65	0.25	1.3	30.3	18.2	4.2	0.3	54.3	5.7	0.1	1.7	35.0	2.9
Postingestion Counts													
5.60	3.40	0.39	3.0	21.5	22.0	6.5	2.0	55.0	4.5	0.0	0.5	39.5	0.5
4.30	3.10	0.27	3.5	20.5	21.5	5.5	0.5	51.5	5.5	0.0	1.0	40.0	2.0
4.30	2.45	0.43	1.5	22.5	29.5	8.0	1.5	63.0	5.5	0.0	2.0	26.5	3.0
5.05	3.40	0.32	2.0	35.0	28.0	6.5	0.0	71.5	0.5	0.0	1.0	26.5	0.5
4.80	3.30	0.31	1.5	21.0	20.0	2.0	0.0	44.5	4.5	0.5	0.0	48.0	2.5
4.55	2.85	0.36	0.5	27.5	19.0	3.0	1.0	51.0	8.5	0.0	2.0	34.5	4.0
6.45	3.00	0.53	0.5	31.5	28.0	9.5	1.0	70.5	1.0	0.5	1.0	24.5	2.5
4.05	3.10	0.23	2.5	30.0	24.0	7.0	1.0	63.5	2.0	0.0	2.5	28.5	3.5
4.20	3.10	0.26	1.0	27.5	16.0	2.5	0.0	47.0	1.5	0.0	1.0	46.5	4.0
5.05	2.95	0.40	2.0	12.0	15.0	4.5	0.5	34.0	3.0	0.0	0.0	60.0	3.0
4.60	3.55	0.22	2.0	36.5	18.5	2.5	0.0	59.5	0.0	0.5	2.5	35.0	2.5
3.30	3.30	0.00	1.5	31.0	17.0	2.5	0.0	52.0	6.0	0.0	0.0	36.0	6.0
4.35	3.00	0.30	1.0	24.0	15.0	2.0	0.0	42.0	16.0	1.0	1.0	37.0	3.0
5.20	3.25	0.37	1.0	27.5	14.0	1.5	0.0	44.0	3.5	0.0	0.0	50.0	2.5
5.25	3.05	0.41	2.0	44.5	28.5	5.0	1.0	81.0	3.5	1.0	0.5	12.0	2.0
3.70	3.00	0.18	0.5	31.5	13.5	2.5	0.5	48.5	8.5	0.0	3.0	38.0	2.0
5.95	3.90	0.34	1.5	35.0	15.5	2.5	0.0	54.5	11.5	0.0	2.0	27.5	4.5
4.15	3.70	0.10	1.0	29.5	16.5	2.5	0.0	49.5	4.0	0.0	3.5	38.5	4.5
5.50	3.20	0.41	0.5	38.5	23.0	3.0	1.5	66.5	14.5	0.5	3.5	13.0	3.0
4.80	3.90	0.18	3.0	36.5	17.5	2.5	0.5	60.0	1.0	0.0	3.0	33.5	2.5
4.05	3.10	0.23	1.0	43.5	16.0	2.0	0.0	62.5	3.5	0.5	2.0	28.5	3.0
5.00	3.10	0.38	0.0	29.0	10.0	2.5	0.0	41.5	27.5	0.0	3.0	26.0	2.0
3.75	3.00	0.20	3.0	57.5	11.5	1.5	0.0	73.5	5.5	0.5	0.0	17.5	3.0
4.95	2.90	0.40	2.0	50.0	11.0	3.0	0.0	66.0	6.5	0.5	2.0	22.0	3.0
4.05	4.00	0.02	2.5	38.0	12.0	2.5	0.0	55.0	7.0	0.0	1.0	32.0	5.0
4.50	3.20	0.28	1.0	42.5	15.0	4.0	0.0	62.5	3.0	0.0	1.5	29.5	3.5
4.10	3.05	0.34	1.5	42.0	16.5	4.0	0.0	64.0	5.0	0.0	1.0	27.0	3.0
4.80	3.70	0.29	4.0	38.5	6.5	0.5	0.0	49.5	9.0	0.0	0.5	39.0	2.0
4.66	3.23	0.30	1.6	32.9	17.9	3.6	0.3	56.3	6.2	0.2	0.1	32.8	2.9

TABLE III. DIFFERENTIAL COUNTS IN TWENTY-FIVE INSTANCES IN WHICH THERE WERE A POSTINGESTION LEUCOCYTE INCREASE AND UNCHANGED OR DIMINISHED LEUCOCYTE FRAGILITY

ACETIC W.B.C.	ACETONE W.B.C.	FRAGILITY INDEX	NEUTROPHILES I	NEUTROPHILES II	NEUTROPHILES III	NEUTROPHILES IV	NEUTROPHILES V	TOTAL NEUTROPHILES	EOSINOPHILES	BASOPHILES	MONONUCLEARS	SMALL LYMPHOCYTES	LARGE LYMPHOCYTES
Fasting Counts													
7.55	4.55	0.39	1.0	15.5	21.5	9.0	4.5	51.5	3.0	0.5	4.0	36.0	5.0
7.00	5.20	0.40	2.0	20.0	31.5	10.5	2.0	66.0	2.5	0.0	2.5	24.0	5.0
5.95	4.40	0.25	1.0	12.5	22.5	7.5	0.5	44.0	6.5	0.0	0.5	47.5	1.5
9.35	5.15	0.44	3.5	49.5	17.0	1.0	0.0	71.0	1.0	0.0	0.0	26.5	1.5
5.75	4.60	0.18	2.5	21.0	11.5	4.5	0.5	40.0	10.0	0.0	1.0	47.5	1.5
5.05	4.40	0.12	1.5	29.5	16.0	4.5	1.0	52.5	5.0	0.5	1.5	38.0	2.5
4.90	4.10	0.16	1.5	41.0	11.0	3.5	0.0	57.0	6.5	0.0	1.5	32.0	3.0
5.85	4.70	0.19	2.5	43.5	13.0	1.5	0.0	60.5	1.5	0.0	2.5	32.5	3.0
7.70	4.90	0.36	3.5	54.5	20.0	3.5	0.0	81.5	0.5	0.0	3.5	13.0	1.5
5.75	5.20	0.09	0.0	22.5	10.0	1.5	0.0	34.0	28.5	1.0	1.5	32.0	3.0
6.45	4.45	0.32	0.5	32.0	13.0	2.5	0.5	48.5	2.5	0.5	0.5	47.0	1.0
7.80	5.00	0.36	2.0	21.0	15.0	3.5	0.5	42.0	12.0	0.0	2.5	40.0	3.5
6.60	4.80	0.29	2.0	39.0	15.5	2.5	0.5	59.5	2.5	0.0	0.5	36.0	1.5
7.80	4.65	0.40	2.0	30.0	12.0	2.0	0.0	46.0	3.0	0.0	3.0	46.5	1.5
8.20	4.50	0.45	2.0	44.5	9.0	2.0	0.5	58.0	3.5	0.0	1.0	35.0	2.5
10.40	5.05	0.52	2.5	58.5	20.5	3.5	0.0	85.0	0.5	0.0	2.0	9.5	3.0
6.75	4.50	0.33	2.0	45.0	7.5	0.0	0.0	54.5	6.5	0.0	2.5	32.0	4.5
7.70	5.40	0.30	1.0	35.5	17.5	7.0	0.0	61.0	4.5	0.0	2.5	31.0	1.0
5.45	4.35	0.20	1.0	32.0	15.5	3.5	0.0	52.0	11.5	0.5	3.5	28.5	4.0
8.00	5.20	0.35	0.0	25.0	19.5	7.5	0.0	52.0	4.5	0.5	2.5	36.0	4.5
5.85	4.35	0.26	1.0	28.0	17.5	2.5	0.0	49.0	12.0	0.0	3.5	32.5	3.0
9.60	5.55	0.42	2.5	46.0	16.5	4.0	0.0	69.0	0.5	0.0	2.0	24.0	4.5
8.60	5.00	0.42	1.0	52.5	13.0	0.0	0.0	66.5	2.0	0.0	0.0	29.0	2.5
8.20	5.10	0.38	0.0	32.0	15.0	4.0	1.0	52.0	1.0	0.0	5.5	37.5	4.0
6.80	4.35	0.36	0.0	27.5	25.5	7.5	1.0	61.5	9.5	1.0	1.0	21.5	5.5
6.80	4.73	0.30	1.8	30.9	16.8	4.3	0.7	54.5	6.3	0.2	1.7	34.8	2.6
Postingestion Counts													
10.00	6.95	0.34	2.0	12.0	21.0	12.0	1.5	48.5	6.0	0.5	1.0	41.0	3.0
11.80	7.15	0.39	3.0	28.0	32.0	9.0	0.0	72.0	2.5	0.0	1.5	22.5	1.5
7.40	5.90	0.20	1.0	17.5	22.0	3.0	0.5	44.0	7.5	0.0	2.5	43.0	3.0
12.60	7.45	0.40	3.0	39.5	20.5	7.5	0.0	70.5	0.5	0.0	1.0	26.0	2.0
6.65	5.90	0.11	1.5	22.5	9.0	2.0	0.0	35.0	6.5	0.0	1.0	55.0	2.5
6.10	5.80	0.04	2.0	32.0	15.0	3.0	0.5	52.5	5.0	0.0	0.0	39.0	3.5
7.60	5.80	0.25	3.0	39.0	11.5	1.5	0.5	55.5	11.5	0.5	1.0	28.5	3.0
8.85	5.90	0.33	2.0	51.5	23.0	1.0	0.0	77.5	2.5	0.5	1.0	17.0	1.5
7.70	7.70	0.00	2.0	43.5	20.0	4.0	0.5	70.0	0.5	0.0	3.0	25.5	1.0
7.80	6.20	0.21	0.0	24.0	12.5	0.5	0.0	37.0	32.0	0.5	0.5	27.5	2.5
8.60	6.70	0.22	1.0	46.5	16.5	4.0	0.0	68.0	6.0	0.0	1.0	24.5	0.5
12.25	8.20	0.33	0.5	35.0	22.5	5.0	0.5	63.5	10.0	1.0	2.0	21.5	2.0
7.60	6.85	0.10	1.0	33.5	21.0	7.5	1.0	64.0	3.5	0.5	4.0	25.5	2.5
9.60	7.10	0.26	2.5	47.0	15.5	2.0	0.0	67.0	1.5	0.0	2.5	27.0	2.0
8.95	6.75	0.25	0.5	30.5	15.5	3.5	0.0	50.0	7.0	0.0	1.5	35.5	6.0
12.80	8.05	0.37	2.5	59.0	17.0	1.5	0.0	80.0	0.0	0.0	3.0	13.5	3.5
7.80	6.65	0.15	2.0	47.5	8.5	0.5	0.0	58.5	8.5	0.0	1.5	28.5	3.0
9.55	6.80	0.29	0.5	37.0	19.0	4.0	0.5	61.0	8.0	0.0	2.0	27.0	2.0
7.90	6.50	0.18	0.5	28.0	22.5	8.5	0.0	59.5	6.0	0.0	2.0	29.0	3.5
10.90	6.40	0.41	1.0	53.5	19.5	3.0	0.0	77.0	2.0	0.0	2.0	16.5	2.5
7.75	6.05	0.22	1.5	52.0	18.0	1.5	0.0	73.0	8.0	0.0	1.0	17.0	1.0
11.00	6.85	0.38	1.0	52.0	21.5	1.0	0.0	75.5	0.5	0.0	1.0	20.0	3.0
8.60	5.00	0.42	1.0	52.5	13.0	0.0	0.0	66.5	2.0	0.0	0.0	29.0	2.5
9.30	6.05	0.35	0.5	52.5	17.0	5.5	0.0	75.5	0.0	0.0	2.5	17.5	4.5
10.75	7.15	0.33	1.5	39.5	28.0	2.5	0.0	71.5	2.5	0.0	4.0	19.0	3.0
9.19	6.63	0.27	1.4	39.0	18.4	3.7	0.2	62.7	5.6	0.1	1.7	27.0	2.6

TABLE IV. COMPARATIVE DIFFERENTIAL COUNTS MADE IN THE FASTING STATE AND FORTY-FIVE MINUTES AFTER INGESTION OF A SINGLE FOOD

	POSTINGESTION LEUCOPENIA (AVERAGE OF 28 COUNTS)				POSTINGESTION LEUCOCYTE INCREASE (AVERAGE OF 25 COUNTS)			
	FASTING		45 MINUTES AFTER INGESTION		FASTING		45 MINUTES AFTER INGESTION	
Acetic white count	6,500		4,660		6,800		9,190	
Acetone white count	5,820		3,230		4,730		6,630	
Fragility index	0.25		0.30		0.30		0.27	
Polymorphonuclear neutrophiles		%		%		%		%
I	81	1.3	74	1.6	122	1.8	129	1.4
II	1,969	30.3	1,533	32.9	2,101	30.9	3,584	39.0
III	1,183	18.2	834	17.9	1,142	16.8	1,691	18.4
IV	273	4.2	168	3.6	292	4.3	340	3.7
V	19	0.3	14	0.3	47	0.7	18	0.2
Total neutrophiles	3,529	54.3	2,623	56.3	3,706	54.5	5,762	62.7
Eosinophiles	370	5.7	289	6.2	422	6.3	515	5.6
Basophiles	32	0.1	92	0.2	14	0.2	9	0.1
Mononuclears	110	1.7	46	0.1	115	1.7	156	1.7
Small lymphocytes	2,275	35.0	1,509	32.8	2,366	34.8	2,481	27.0
Large lymphocytes	188	2.9	135	2.9	176	2.6	239	2.6

clear leucocytes or to any increase in the relative numbers of older cells. On the other hand, when postingestion leucocytosis is present, the data indicate that a relative and absolute increase occurs in the number of younger polymorphonuclear leucocytes as judged by nuclear lobulations. This increase in presumably younger cells is accompanied by a diminution in leucocyte fragility.

SUMMARY

1. A method is described by which estimates can be made of white cell fragility roughly comparable to the estimation of red cell fragility in hypotonic saline.

2. Evidence is presented to show that the transitory leucopenia seen following the ingestion of certain foods is accompanied by increased fragility of leucocytes.

3. This increased fragility does not appear to be caused by a change in the relative proportions of the different types of white cells.

4. It may well be the result of some alteration in the white cell membrane.

5. No conclusion as to whether this change results from an antigen-antibody reaction or from chemical or mechanical trauma can be made from the present data.

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SOME ANTIANAPHYLACTIC AND ANTIHISTAMINIC PROPERTIES OF N'PYRIDYL, N'BENZYL, DIMETHYLETHYLENEDIAMINE MONOHYDROCHLORIDE (PYRIBENZAMINE)*†

CARL E. ARBESMAN, M.D., GEORGE F. KOEPF, M.D., AND GEORGE E. MILLER, M.D., BUFFALO, N. Y.

SINCE Dale and Laidlaw[1] described the many similarities between histamine and anaphylactic shock, the search for methods and substances to prevent these conditions has been under intensive investigation. Hill and Martin,[2] in 1932, reviewed this subject and listed 165 methods of inhibiting anaphylaxis. Dragstedt[3] in an extensive review on anaphylaxis in 1941 concluded that the tissue liberation of histamine, heparin, and possibly a choline occurs during anaphylactic reactions in various animals. Within the past decade the amino acids, arginine, histidine, and cysteine, were shown to have certain antihistaminic and antianaphylactic properties.[4-8] Landau and Gay[9] noted that arginine (2 per cent solution injected intracutaneously) failed to affect the skin reaction of a sensitive patient to a specific pollen extract. Histamine,[10, 11] histamine azoprotein,[12] and histaminase[13] also have been thoroughly studied and reported to be antihistaminic and antianaphylactic.

Bovet and Staub,[14] in 1937, studied a group of compounds in the Fourneau series of chemicals and found two which had marked antihistaminic and antianaphylactic properties. These substances, thymoxyethyldiethylamine and N'phenyl, N'ethyl, N'diethyl-ethylenediamine, were designated 929F and 1571F, respectively. Another compound, N'dimethylamine ethyl N'benzylanilene (also known as 2339 RP and antergan), was investigated by many European workers.[15-21] This drug was found to be more effective and less toxic than 929F and 1571F, and, hence, it was used clinically in the treatment of various allergic disorders. Promising results were reported. Parrot[15] noted that 2339 RP decreased the size of histamine wheals in human beings. More recently, Loew, Kaiser, and Moore[22] and Loew and Kaiser[23] described a series of benzhydryl ethers and amines. One of these, β-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl), was found to have the most potent antihistaminic and antianaphylactic properties of this series. It was also the least toxic. Mayer, Huttrer, and Scholz[24] investigated several amino pyridyl and amino picoline derivatives related to 1571F and found that one of these, N'pyridyl, N'benzyl, dimethylethylenediamine monohydrochloride (Pyribenzamine) was highly effective orally or parenterally against anaphylactic and histamine shock. In addition, the toxic dose was shown to be many times the protective dose. Mayer[25] compared many of these recently synthesized antihistaminic and antianaphylactic

*From the Department of Bacteriology and Immunology, University of Buffalo School of Medicine, and the Buffalo General Hospital.

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substances and concluded that pyribenzamine appeared to be the most potent of these drugs. It was highly active in vitro and in vivo against various histamine effects as well as in vivo in active anaphylaxis. Because of its apparent superior effect, it seemed desirable to extend the studies with pyribenzamine.

THE EFFECT OF PYRIBENZAMINE ON ALLERGIC STUDIES IN ANIMALS AND IN MAN

The Effect of Pyribenzamine on Passive Anaphylaxis in Guinea Pigs.—Twenty-four guinea pigs weighing from 250 to 350 grams were passively sensitized intraperitoneally with 1 c.c. of antihuman rabbit serum.* Forty-eight hours later all 24 guinea pigs were given an intracardiac injection of 1 c.c. of human serum (the shocking dose). Ten to thirty minutes prior to administration of the shocking dose, 20 of the 24 guinea pigs were injected intraperitoneally with various doses of pyribenzamine (Table I). All 4 of the untreated animals died in typical anaphylactic shock within two minutes. Eight guinea pigs were given 1 mg. per kilogram of pyribenzamine intraperitoneally fifteen minutes prior to the shocking dose. One of these developed typical fatal shock, 2 developed severe shock but recovered, 1 showed moderate symptoms, 3 showed very minimal symptoms, and 1 showed no symptoms whatsoever. Hence, 50 per cent of these animals were adequately protected by 1 mg. per kilogram of pyribenzamine. When 1.5 mg. per kilogram of pyribenzamine were given to 8 guinea pigs, 6 of them developed no symptoms, one developed minimal symptoms, and one died. With 2 mg. per kilogram of pyribenzamine 2 of the 4 guinea pigs remained normal and the other 2 had slight symptoms. Since, however, there were but four instances in which 2 mg. of the drug prevented death, while with 1 mg. only one of 8 pigs died, it cannot be rightly inferred that 2 mg. will give complete protection until this is confirmed by a larger series.

TABLE I. EFFECT OF PYRIBENZAMINE ON PASSIVE ANAPHYLAXIS IN GUINEA PIGS

NUMBER OF SENSITIZED GUINEA PIGS SHOCKED WITH INTRACARDIAC INJECTION OF 1 C.C. OF HUMAN SERUM	PYRIBENZAMINE MG./KG.	RESULTS* DEGREE OF SHOCK OBTAINED				
		++++	+++	++	+	0
4	0	4	0	0	0	0
8	1.0	1	2	1	3	1
8	1.5	1	0	0	1	6
4	2.0	0	0	0	2	2

*Fatal shock, ++++; severe shock with recovery, +++; moderate, ++; slight symptoms, +; no symptoms, 0.

The Effect of Pyribenzamine on Precipitin Titer.—One-tenth cubic centimeter of antibody (undiluted antihuman rabbit serum) was placed into each of 12 test tubes. To 6 of the tubes was added 0.25 c.c. of normal saline and to the remaining 6 tubes was added 0.25 c.c. of a 1 per cent solution of pyribenzamine (2.5 mg.) To each set of six test tubes 0.25 c.c. of identical serial dilutions of antigen (human serum) was then added. The mixtures were shaken and incubated at 37° C. The degree of precipitation was recorded at the end of one hour and three hours (Table II). The addition of pyribenzamine caused no demonstrable difference in the precipitin titer.

*This serum was prepared by injections of human serum into rabbits three times weekly for four weeks until the precipitin titer on trial bleeding was at least 1:10,000.

TABLE II. EFFECT OF PYRIBENZAMINE ON PRECIPITIN TITER IN VITRO

DILUTION OF ANTIGEN (HUMAN SERUM) 0.25 C.C.	UNDILUTED ANTIHUMAN RABBIT SERUM (0.1 C.C.) (ANTIBODY) PLUS			
	0.25 C.C. SODIUM CHLORIDE		0.25 C.C. PYRIBENZAMINE (1% SOLUTION)	
	1 HR.	3 HR.	1 HR.	3 HR.
1:5	++++	++++	++++	++++
1:50	+++	+++	+++	+++
1:500	+	++	++	+++
1:5,000	0	+	+	+
1:50,000	0	0	+	+
0 Saline	0	0	+	+

TABLE III. EFFECT OF PYRIBENZAMINE ON COMPLEMENT TITER IN GUINEA PIG SERUM

DILUTION OF GUINEA PIG SERUM	SENSITIZED SHEEP CELLS (0.4 C.C.) PLUS					
	GUINEA PIG SERUM (0.2 C.C.) BEFORE PYRIBENZAMINE TIME OF INCUBATION			GUINEA PIG SERUM (0.2 C.C.) ½ HR. AFTER 5 MG. OF PYRIBENZAMINE TIME OF INCUBATION		
	70 MIN.	90 MIN.	155 MIN.	70 MIN.	90 MIN.	155 MIN.
1:10	-	-	-	-	-	-
1:20	-	-	-	-	-	-
1:40	+	+	+	+	+	-
1:80	++	++	++	+	+	+
1:160	++++	++++	++++	++++	++++	++++
1:320 to 1:2,560	++++	++++	++++	++++	++++	++++
0	++++	++++	++++	++++	++++	++++

TABLE IV. EFFECT OF PYRIBENZAMINE ON SIZE OF HISTAMINE WHEALS IN HUMAN BEINGS

(Change in size of skin reaction, or end point* forty-five minutes after ingestion of Pyribenzamine [50 to 150 mg.])

NUMBER OF PATIENTS	NO CHANGE	INCREASE	DECREASE
Normal (22)	6	2	14
Allergic (6)	1	1	4
Total (28)	7	3	18

*Minimum dilution of histamine which produces a significant reaction (1 plus to 2 plus).

The Effect of Pyribenzamine on Guinea Pig Complement Titer.—Blood serum was obtained from guinea pigs weighing 500 grams before and one-half hour after the intraperitoneal injection of 5 mg. of pyribenzamine. The complement titer of these sera was then determined. As can be seen in Table III, there was no change in the complement titer following pyribenzamine injection.

The Effect of Pyribenzamine on Histamine Wheals in Human Beings.—Serial dilutions of histamine were given intradermally to normal subjects and allergic patients. Fifteen minutes later the outlines of the wheals and erythematous flares were traced on transparent paper. All subjects were then given pyribenzamine (50 to 150 mg.) orally, and forty-five minutes later they were retested with the same dilutions of histamine in comparable sites on the opposite arm. The reactions were again traced in fifteen minutes. Tracings of histamine wheals before and after pyribenzamine in both normal and allergic

individuals are shown in Fig. 1. Fourteen of 22 subjects and 4 of 6 allergic patients showed a definite decrease in the size of the wheal after pyribenzamine administration (Table IV). Yonkman and co-workers[26] studied the effect of pyribenzamine on histamine skin wheals in albino rabbits and found that 1 mg. per kilogram intravenously had a definite and constant antihistaminic effect on the wheals. When pyribenzamine was given orally, however, 250 to 400 mg. per kilogram were needed to produce the same effect. The small effective intravenous dose as compared with the large effective oral dose in rabbits suggests that lack of absorption of adequate amounts might account for the inconstant effects noted in human beings.

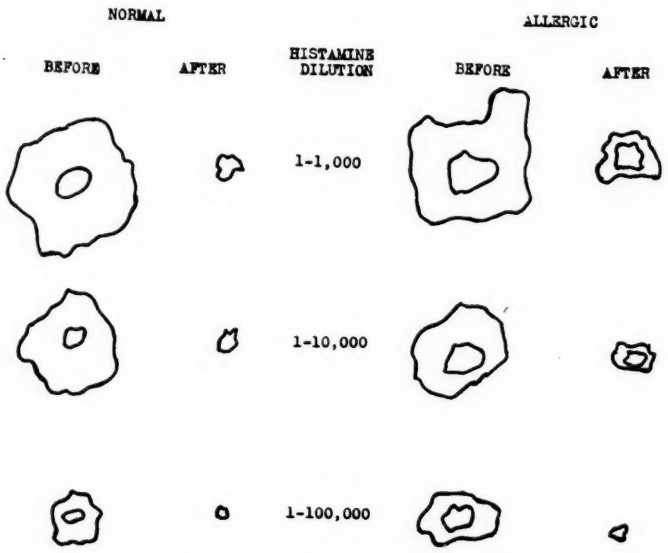

Fig. 1.—Effect of pyribenzamine on histamine wheals in human beings.

The Effect of Pyribenzamine on Allergic Wheals.—Intradermal tests with serial dilutions of allergens* were performed on 24 patients, and the reactions were traced fifteen minutes later. On the same day, forty-five minutes after 100 mg. of pyribenzamine had been given orally, the patients were retested with the same allergens in the same dilutions on comparable sites of the opposite arm and the results were again traced. The tracings obtained on 2 patients, before and after pyribenzamine, are shown in Fig. 2. Fourteen of the 24 patients showed a decrease in reactivity after pyribenzamine (Table V).

TABLE V. EFFECT OF PYRIBENZAMINE ON SIZE OF ALLERGIC WHEALS IN HUMAN BEINGS

(Change in size of skin reaction or end point* forty-five minutes after ingestion of Pyribenzamine)

NUMBER OF PATIENTS	NO CHANGE	INCREASE	DECREASE
24	7	3	14

*The minimum dilution of allergen which produces a significant positive skin reaction (1 plus).

*Allergens used were extracts of ragweed pollen, timothy pollen, dog dander, cat dander, and the fungus of *alternaria.*

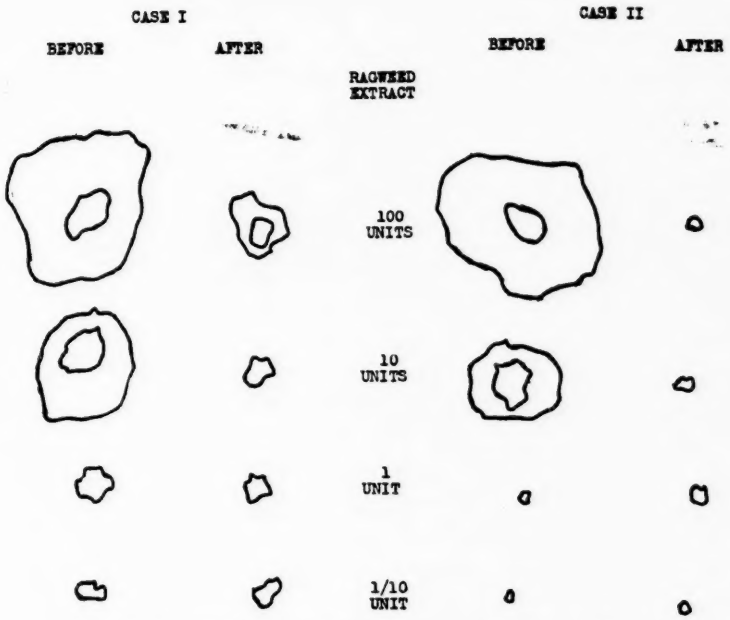

Fig. 2.—Effect of pyribenzamine on allergic wheals.

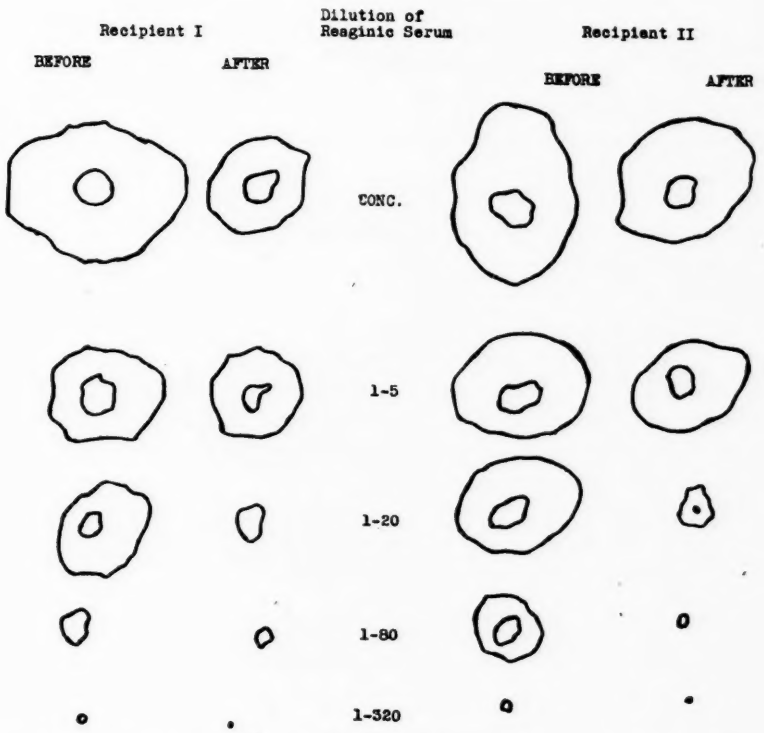

Fig. 3.—Effect of pyribenzamine on passively sensitized sites in human beings.

The Effect of Pyribenzamine on Passively Sensitized Skin Sites.—Duplicate serial dilutions of a serum containing a high titer of cottonseed reagins were injected intradermally (0.1 c.c.) on comparable skin sites of each upper arm of 6 normal subjects. The sites were marked. Twenty-four hours later each site on the right arm was injected intradermally with a constant amount of cottonseed extract (0.01 c.c.) of 1,800 protein nitrogen units per cubic centimeter. The reactions were traced fifteen minutes later. The subjects were then given 100 mg. of pyribenzamine orally. One hour later, each site on the left arm was injected with the same cottonseed extract and the results were again traced in fifteen minutes. There was a definite decrease in the size of the reactions after pyribenzamine, and it required a higher concentration of serum to produce a positive reaction after pyribenzamine (Fig. 3).

SUMMARY

1. Pyribenzamine has potent antianaphylactic activity as demonstrated by passive anaphylactic experiments in guinea pigs.

2. Pyribenzamine has no demonstrable effect on precipitin titer.

3. Pyribenzamine has no demonstrable effect on the complement titer of guinea pigs.

4. Pyribenzamine administered orally to human beings decreased the size of histamine skin wheals in 18 of 28 subjects.

5. Pyribenzamine (oral) diminished the skin reactivity in 14 of 24 allergic patients.

6. Pyribenzamine reduced the reactivity of skin sites passively sensitized with serum containing cottonseed reagins.

We wish to thank Miss Anne Heide for her technical assistance.

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CLINICAL EXPERIENCES WITH A NEW ANTIHISTAMINIC DRUG*†

CHARLES H. EYERMANN, M.D., ST. LOUIS, MO.

β-dimethylaminoethyl benzhydryl ether hydrochloride‡ is a synthesized drug of low toxicity belonging to the pharmacologic group having the property of preventing some of the effects of histamine. It was first described and studied by Loew, Kaiser, and Moore,[1] who showed that it alleviated the symptoms and diminished the mortality in guinea pigs which had been administered histamine as a mist and intravenously. In a later study,[2] it was shown that the drug was markedly effective in alleviating anaphylactic shock. It was possible to observe its effect upon the following clinical situations.

POLLINOSIS

There were 52 cases of pollinotic vasomotor rhinitis. Those who were under continuous observation were given the drug when they were subjectively uncomfortable; those who appeared for the first time, were given it at that time. In the cases of grass pollinosis, it was given when it was available (Table I).

TABLE I. DOSAGE—POLLINOSIS

Due to:	HELPFUL	? HELPFUL	FAILURE
Grasses	4		
Ragweed	31	12	5
	35	12	5
	(67+ %)	(23+ %)	(9+ %)
Comfortable with:			
50 mg. once a day	5	Cases classed as ? helpful and failure received 50 mg. four times a day	
50 mg. A.M. and P.M.	14		
50 mg. every four to eight hours	16		
	35		

The effect of the drug was classified as helpful when all discomfort was ameliorated, 35 cases (67 per cent); as questionably helpful when only some of the discomfort was ameliorated, 12 cases (23 per cent); and as failure when all the discomforts of the vasomotor rhinitis persisted, five cases (9 per cent). The patients were instructed to take 50 mg. at that period of the twenty-four hours when they expected the most discomfort and to take further doses of 50 mg. as needed for discomfort, at four- to eight-hour intervals. Of the 35 patients who had satisfactory relief, five had it with one 50-mg. capsule during twenty-four hours; 14 had relief with 50 mg. night and morning; the remaining 16 required 50 mg. at intervals of four to eight hours. Some of these

*From the Department of Internal Medicine, Washington University, and The Barnes Hospital, St. Louis.

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began with 50 mg. a day, increased the dosage with the advancing season, and decreased it as the symptoms disappeared or as the season waned. Patients reported that improvement began in twenty to thirty minutes when taken for and during acute episodes, and in several instances it was possible to observe the transition from bleary, streaming eyes, nasal blocking and coryza, and attendant ancillary discomforts to complete comfort in twenty minutes after the oral administration of 50 milligrams. The drug was discontinued when the patients no longer felt the need for it; the period over which it was taken varied from five to thirty-five days for the various patients with seventeen days as the average.

An analysis of the length of time these patients had had pollinosis, the degree of sensitivity, the influence of hyposensitization injections (either in the past or this season), sex, or frequency of dosage gives no explanation for the fact that some patients needed the drug only five to seven days, while others needed it for thirty-five days. Although gaining relief from the presenting symptoms, one patient discontinued the drug after three days on account of dizziness. It does appear, however, that the earlier in the season the drug is started the longer it will be needed.

In 12 instances the drug was classified as questionably helpful because all symptoms were not ameliorated; in seven of these, there was no sneezing, but the nasal blocking was unaffected; in four there was less sneezing and nasal blocking with the development of chest oppression and/or wheezing while taking the drug; and in one instance there was relief from sneezing and blocking for only the first two days of therapy. Purulent nasal discharge was present in six of these patients.

An analysis of the five unbenefited cases shows no common factor that might account for the ineffectiveness of the drug. All five patients were women, their ages ranging from 17 to 45 years; all were sensitive to 10 protein nitrogen units per cubic centimeter of ragweed, and all but one were sensitive to allergens other than ragweed. Purulent nasal discharge was identified in four instances.

By titration, 12 patients were found to be sensitive to 1 PNU per cubic centimeter; 9 (75 per cent) of these were helped. Twenty-seven reacted to 10 PNU per cubic centimeter; 15 (55 per cent) of these were helped. Seven were sensitive to 100 PNU per cubic centimeter; five (70 per cent) were helped. Two reacted to 1,000 PNU per cubic centimeter; both were helped.

There were side reactions in 20 cases: somnolence in 10 instances; "dry" nose in 5; vertigo in 3; nausea in 2; weakness and nervousness in 2 instances each; palpitation, insomnia, and abdominal cramping in one instance each; somnolence, vertigo, and palpitation combined in one instance; somnolence and weakness combined in two; nausea and abdominal cramping combined in one; and "dry" nose and vertigo combined in one. In one instance the drug had to be discontinued because somnolence interfered with work, and, in another, it was stopped because of dizziness. In a few cases, the symptoms disappeared when the dosage was reduced but reappeared when it was increased again. In all other instances, these side effects became less with continuation of the drug in the same dosage (Table II).

TABLE II. SIDE REACTIONS

20 patients {15 females, 40+ %} {5 males, 33+ %}

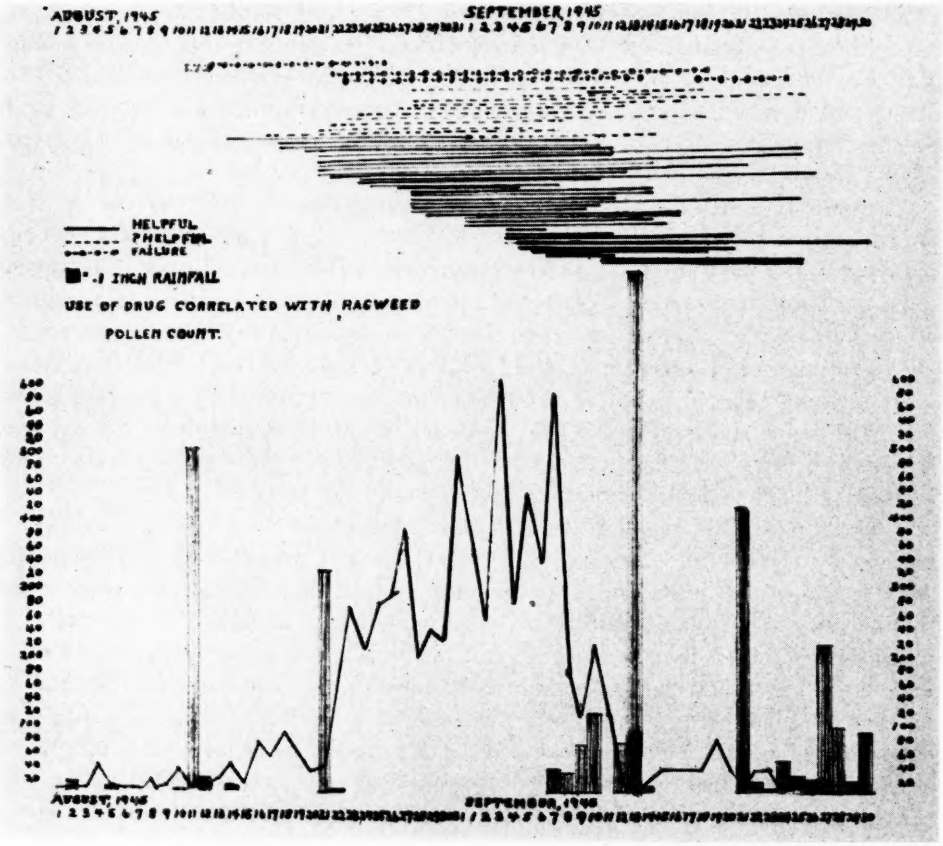
Somnolence	10 times	Somnolence }	
Dry dose	5 times	Vertigo }	1 time
Vertigo	3 times	Palpation }	
Nausea	2 times	Somnolence and weakness	1 time
Weakness	2 times	Somnolence and nausea	1 time
Nervousness	2 times	Dry nose and vertigo	1 time
Palpation	1 time	Nausea and abdominal cramping	1 time
Insomnia	1 time		
Abdominal cramping	1 time		

No Side Reactions

32 patients {22 females, 59+ %} {10 males, 66+ %}

Four cases were due to the pollen of the grasses. The drug was given from July 11 to July 30, 1945. During this time the grass count was low (10 more or less) and there was no rain. All four patients were comfortable with 50 to 100 mg. a day.

TABLE III



Forty-eight cases were due to the pollen of ragweed. The drug was begun as early as August 11 and as late as Sept. 18, 1945. Thirty-one patients (64 per cent) were completely relieved. It was questionably helpful in 12 cases (25 per cent), and in five (10 per cent) it was a failure. The purposeful omission of the drug in several cases in which it was helpful resulted in prompt recurrence of the vasomotor rhinitis, which was again controlled by the resumption of the drug. Ragweed pollen appeared on the atmospheric slides on July 30, reached its greatest concentration in early September, and receded to low concentrations after September 13. There was no rain during the period of the most active pollination (Table III).

WHEEZING DYSPNEA

Seven patients with active pollinosis developed wheezy breathing while taking 50 mg. three to four times a day; two were relieved by further doses of 50 to 100 mg.; in the remainder, the wheezing was uninfluenced by similar dosages. Purulent sputum or nasal discharge as evidence of infection was present in one of the two relieved and in two of those not relieved; in the remainder of those unrelieved, there is no data on one and the other two had no purulent discharges.

There were nine other instances of bronchial asthma: three, extrinsic (all sensitive to several inhalants); four, extrinsic and intrinsic (three of these being sensitive to aspirin, the other to orrisroot; all having either chronic upper and/or lower respiratory tract infection); and two, intrinsic. In four cases (three extrinsic, one intrinsic), 50 mg. to 100 mg. relieved mild wheezing but not as promptly or as effectively as 0.03 Gm. of ephedrine did, and the drug was ineffective in that dosage for severer bronchospasm.

In two instances (idiosynerasy to aspirin) bronchospasm was increased and adrenalin was required for relief; the remainder of the patients were unbenefited (Table IV).

TABLE IV. WHEEZING DYSPNEA

ETIOLOGY	NUMBER OF CASES	RELIEVED MILD WHEEZING	NO BENEFIT
Extrinsic	10	5	5
Extrinsic and intrinsic	4		4
Intrinsic	2	1	1
Relief neither as prompt nor as effective as with 0.03 Gm. of ephedrine No severe episodes relieved by 100 mg. orally			
Bronchospasm was increased in 2 cases—both were hypersensitive to aspirin and had chronic upper and lower respiratory tract infection			

CHRONIC URTICARIA

There were 14 instances of chronic urticaria (duration, two months to fifty years): in seven, the cause was undetermined; three were classified as estrogenic urticaria; one was due to aspirin; one, to hypothyroidism; one, to focal infection; and one, to insect bites (duration one week). The drug eased the itching in twenty to thirty minutes coincident with gradual subsidence of the whealing; the erythema persisted for several hours (under direct observation in two

cases). In nine cases, the urticaria was controlled with 50 mg., once or twice a day; in three patients the urticaria required increasing frequency of dosage (150 mg. to 250 mg. during twenty-four hours) to maintain the comfort attained by 50 mg. for twenty-four hours when first given. In one case due to focal infection the whealing, but not the erythema, improved with 50 mg. twice a day. In the whealing due to insect bites, there was complete failure to influence the itching and whealing with a dose of 50 mg., three times a day. Temporary somnolence in three cases and weakness and faintness in one case occurred as side reactions (Table V).

TABLE V. URTICARIA

ETIOLOGY	NUMBER OF CASES	EFFECTIVE	? EFFECTIVE	FAILURE
Undetermined	7	7		
Estrogenic	3	3		
Drug	1	1		
Hypothyroid	1	1		
Insect bites	1			1
Focal infection	1		1	
Total	14	12	1	1

OTHER CONDITIONS

There were four patients with nonseasonal allergic vasomotor rhinitis; all were sensitive to inhalants including house dust. All symptoms were controlled in three with 50 mg., three times a day; in one, the sneezing, but not the nasal blocking, was controlled; this patient also has chronic upper respiratory tract infection.

There were 5 instances of primary nasal polyposis; none of these were benefited by the drug; in 1, there was greater nasal blocking with 50 mg., three times a day.

The migraine and dysmenorrhea of 1 patient who had pollinosis and the vernal conjunctivitis of another were not ameliorated by 50 mg., three times a day (Table VI).

TABLE VI

SUMMARY: 91 CASES	NUMBER OF CASES	EFFECTIVE	? EFFECTIVE	FAILURE
Pollinosis:				
Grasses	4	4		
Ragweed	48	31	12	5
Asthma:				
Extrinsic	10	5*		5
Extrinsic and intrinsic	4			4
Intrinsic	2	1*		1
Allergic nonseasonal vasomotor rhinitis	4	3	1	
Nasal polyposis	4			4
Urticaria	14	12	1	1
Vernal conjunctivitis	1			1
Total	91	56	14	21
Migraine	1†			1
Dysmenorrhea	1†			1

*Effective only in mild wheezing and not as effective as 0.03 Gm. of ephedrine.
†Occurred in patient with pollinosis for which it was effective.

DISCUSSION

According to present knowledge, the use of this drug is based on satisfactory experimental grounds. It is markedly effective in alleviating anaphylactic shock and diminishes the mortality in guinea pigs which have absorbed histamine either as a mist or intravenously. Apparently, the drug accomplishes this effect by inhibiting the contractions of smooth muscle without influencing the associated symptoms of histamine or anaphylactic shock.

Obviously, this series is too small to yield statistically significant results, but the palliative effects in nearly all instances of urticaria and in a high percentage of pollinotic vasomotor rhinitis lends support to the hypothesis that histamine or histamine-like substance is released during an allergic reaction. However, the relief of symptoms is not conclusive proof that they are due to histamine. The instances of allergic vasomotor rhinitis wherein the itching and sneezing were controlled but the turgescence of the turbinates was uninfluenced and the instances of its ineffectiveness in wheezing dyspnea, despite the experimental evidence of its inhibitory effect on smooth muscle contraction, suggest that factors other than histamine are responsible for the total clinical picture and point to new avenues of thought and experimental research. Bearing on this point may be the fact that higher doses of protecting substances are required to prevent anaphylactic effects than are required to prevent histamine effects.

SUMMARY

1. β-dimethylaminoethyl benzhydryl ether hydrochloride completely relieved the symptoms of pollinotic vasomotor rhinitis in 35 of 52 patients (67 per cent); relieved the sneezing, but not the other associated symptoms in 12 of this group (23 per cent); and failed to relieve any symptoms in 5 (9 per cent). The symptoms recurred promptly when the drug was stopped.

2. The drug completely relieved 12 of 14 patients with chronic urticaria; symptoms recurred when the drug was stopped.

3. The drug, in 50 mg. doses, administered orally, relieved mild wheezing dyspnea in 5 of 16 patients (31 per cent), but the relief was neither as prompt nor as effective as that caused by oral administration of 0.03 Gm. of ephedrine. No severe episodes were relieved by oral administration of 100 milligrams.

4. Three of 4 patients with perennial vasomotor rhinitis were relieved of all symptoms, but they recurred when the drug was stopped.

5. Primary nasal polyposis, vernal conjunctivitis, dysmenorrhea, and migraine were not benefited.

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2. Loew, E. R., and Kaiser, M. E.: Alleviation of Anaphylactic Shock in Guinea Pigs With Synthetic Benzhydryl Alkamine Ethers, Proc. Soc. Exper. Biol. & Med. **58**: 235, 1945.

1102-634 N. GRAND.

DISCUSSION

DR. LOUIS TUFT, Philadelphia.—I think if we could go back a few years and think of the time when ephedrine was first introduced, we could probably duplicate the results that the various authors have discussed. The effects were good in hay fever and possibly in urticaria and not so good in asthma. There is also some reason to feel that certain of these effects resemble those of ephedrine. Such toxic side effects of this drug as irritability, palpitation, insomnia, or drowsiness, are similar to those resulting from ephedrine. I was impressed with Dr. Arbesman's demonstration of the effect of the drug (N'pyridil, N'benzyl, dimethylethylenediamine-hydrochloride) on the wheal and the reduction of the wheal while using it. Some years ago we demonstrated exactly the same effect from the use of adrenalin or aminophylline. I wonder if one of the authors would like to discuss the chemical or pharmacologic relationship that may exist between drugs like adrenaline and ephedrine, as contrasted with the drugs that have just been considered, because there seems to be a resemblance in their pharmacologic action and in their clinical effect.

Original Articles

HISTAMINE ANTAGONISTS

II. Summary of Developments in Nonspecific Inhibition of Histamine, Anaphylaxis, and Allergy

Samuel M. Feinberg, M.D., Chicago, Ill.

THE resemblance of the manifestations of asthma and hay fever to some of the clinical phenomena of anaphylaxis led early in this century to the concept of allergy to explain these symptoms in man. Following the demonstration of specific desensitization or antianaphylaxis in animals, the concept of desensitization by the employment of small doses of the specific allergen was adopted as a therapeutic approach in human hypersensitiveness. Almost from the very beginning of studies in anaphylaxis a search has been going on for a nonspecific method which might inhibit anaphylaxis of any specific origin, with the hope that such a method would serve as a general therapeutic procedure in allergic manifestations.

ANTIANAPHYLAXIS

Up to 1932,[1] there were described at least 165 such substances or methods for which inhibition of anaphylaxis had been claimed. Among these may be mentioned atropine, chloral hydrate, ether, barium chloride, barium sulfate, heparin, sodium bicarbonate, reduction in barometric pressure, benzene in large doses, intercurrent infection with tubercle bacilli, and desensitization with an unrelated antigen to which the animal was also sensitive. While some of these methods had a certain degree of efficiency, they were either too toxic, impractical or insufficiently effective.

In the last few years, a number of other methods for the inhibition of anaphylactic shock and allergic manifestations have been proposed.[2] The common use of potassium salts and sodium thiosulfate in clinical allergy has led Carlson and Whitehead[3] to investigate these substances experimentally. They were found to have very little effect. While some benefit has been claimed by a few workers from the use of vitamin C injected into guinea pigs prior to anaphylaxis,[4] many other workers have failed to confirm these claims. The benefit from vitamin C in allergic conditions has been found practically nil.[5] Although veronal, pernocton, or avertin had some inhibiting effect on anaphylaxis, the effective dose was always toxic and frequently lethal.[6] The protective effect of vitamin P on anaphylactic phenomena[7] awaits further experimentation. The widely publicized claims for ethylene disulfonate in asthma and other allergy led to experiments on anaphylaxis, in which this drug was found to be essentially without protective effect.[8]

From the Division of Allergy, Department of Medicine, Northwestern University Medical School.

ROLE OF HISTAMINE

The role of histamine in anaphylaxis has been the object of study and discussion since Dale and Laidlaw,[9] in 1911, claimed that the injection of histamine into animals caused typical symptoms of anaphylactic shock. Later, Lewis[10] showed that the triple local response in man, displayed after injury to the skin by physical, thermal, chemical, or allergenic agents, is identical with the local manifestations produced by the intracutaneous injection of histamine. Many of the subsequent experimenters corroborated these general claims while others pointed out differences between histamine effects and those of anaphylactic shock and allergy. Dragstedt and Gebauer-Fuelnegg[11] demonstrated that histamine is liberated during anaphylaxis in the intact animal, and Dragstedt and Mead[12] showed that the amount of histamine liberated in dogs after anaphylactic shock was sufficient to explain the severity of the manifestations. The question of the normal origin of the histamine was conclusively demonstrated by Best and his co-workers,[13] who showed it to be a normal constituent of many tissues. Dragstedt summarizes[14] the reasons for considering the active substance as histamine. It is dialyzable, stable to boiling with hydrochloric acid, and inactivated by incubation with diamine oxidase or histaminase and by condensation with diazotized sulfanilic acid. Its contracting effect on the guinea pig intestine is inhibited by arginine (and other more recent and more specific antihistaminic drugs). It lowers the blood pressure of etherized, atropinized cats and produces histamine-like wheals in the human skin.

Practically everyone admits that histamine alone cannot explain all the manifestations of anaphylactic shock, and perhaps those of allergy. The incoagulability of the blood has been attributed to the liberation of heparin. There remain other manifestations of anaphylaxis and allergy which make the histamine concept incomplete. Most observers are, however, in agreement that histamine activity is an important part of the anaphylactic, and probably the allergic, reaction, but that undoubtedly other physiologic changes are also at work.

AMINO ACIDS

The last few years have witnessed a more concerted effort in the attempt to discover means for the prevention of hypersensitiveness. In this approach there has been a great tendency to link the histamine reaction with that of anaphylaxis, on the assumption that when histamine antagonists will have been found they will also serve as inhibitors of anaphylaxis and allergy. Edblacher and his coworkers,[15] in 1937, showed that histidine, cysteine, and arginine inhibited the histamine contraction of the guinea pig intestine. Ackermann and Wasmuth,[16] in 1939, described the inhibiting effect or arginine on the specific contraction of the intestine in sensitized guinea pigs, and Linneweh claimed[17] that this substance inhibits anaphylactic shock in that animal. Mackay[18] and Halpern[19] also noted the inhibiting effect of histidine on histamine reactions.

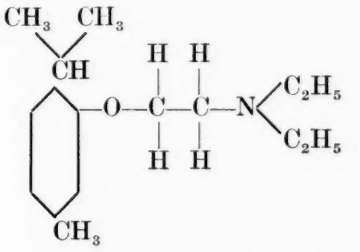
Landau and Gay[20] recently reinvestigated the action of these substances. The inhibition of histamine or antigen contraction on the intestinal strip by the

previous addition of arginine or histidine was corroborated by them. Although death from histamine could be prevented by arginine given intraperitoneally or intracardially, all animals showed some histamine symptoms. Larger doses of arginine caused a high percentage of fatal toxic reactions. In contrast to the observations of Linneweh, these experimenters found that anaphylactic shock was not prevented by arginine. In man, a 2 per cent arginine solution given intracutaneously failed to produce any effect on the pollen reaction in sensitive subjects, when injected into the wheal or combined with the pollen.

It is evident from the above, and other work, that although exerting some action in inhibiting anaphylactic or histamine activity, these amino acids cannot be regarded as useful because of their low index of efficiency and their marked toxicity.

FOURNEAU SYNTHETIC ANTAGONISTS

A more promising approach to this problem was initiated by Fourneau and his followers by the use of certain synthetic compounds. As early as 1910, Fourneau prepared phenolic ethers of aminoalcohols, but their study was abandoned because it was thought that they provoked cardiac symptoms. From 1929 to 1932, Anan and Okasaki studied the sympatholytic action of thymoxyethyldimethylamine. In 1933, Fourneau and Bovet[21] demonstrated that other phenolic ethers have the ability to counteract the action of histamine in vivo and in vitro. The most effective of these was



929F

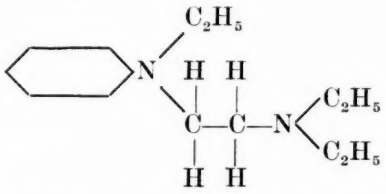
2-isopropyl-5-methylphenoxyethyldiethylamine
(thymoxyethyldiethylamine)

This compound was subsequently labeled 929F. It was shown by Bovet and Maderini[22] that this substance had an ergotoxine-like action on the reversal of the pressor effect of epinephrine on anesthetized dogs. Staub and Bovet,[23] in 1937, reported that 929F was capable of preventing anaphylactic shock in animals.

Climenko and his associates,[24] in 1941, described their pharmacologic experiments with this drug. It could protect guinea pigs from two lethal doses of parenterally administered histamine. The drug was found to be very toxic, producing fall in blood pressure, dyspnea, soreness of muscles, headaches, and other alarming symptoms. In guinea pigs the oxytocic effect of barium chloride and acetylcholine, as well as that of histamine, could be prevented. They concluded, therefore, that this substance was not specific against histamine activity.

However, the studies of Rosenthal and Brown[25] are somewhat at variance with those of the above. They confirmed the inhibiting effect, in vivo and in vitro, on histamine and anaphylactic reactions, but could obtain practically no inhibition of the action of acetylcholine, sodium sulfocyanate, tyramine, sodium bicarbonate, and potassium chloride. In addition to its antihistaminic action, Rosenthal and Minard[26] demonstrated the local anesthetic action of 929F, with a potency twice that of novocain. They cited these findings in support of their thesis that it is the local liberation of histamine which gives rise to the sensation of cutaneous pain.

The phenolic ethers were apparently too toxic, and Staub[27] turned her attention to another series of Fourneau compounds having the ethylenediamine radical. The most promising of these was



1571F

N-phenyl-N-ethyl-N′-diethylethylenediamine

This compound 1571F also had an antihistaminic and antianaphylactic effect. Staub showed that neither 929F nor 1571F had any effect on the skin reaction to histamine. Wilcox and Seegal[28] performed extensive experiments with 1571F. They found that, in guinea pigs, protection against two to six minimal lethal doses of histamine could be obtained by the prior administration of 1 to 4 mg. of this compound, although the animals showed evidence of prostration, cyanosis, increased muscle tonus, and clonic convulsive movements. In sensitized guinea pigs, 17 out of 21 were protected against anaphylactic death from the injection of two to four minimal lethal doses of the antigen, when 1 to 5 mg. of the drug were administered. In the perfused guinea pig heart 0.1 mg. of 1571F per liter of perfusion fluid prevented the usual decrease in coronary flow on the addition of histamine. Similar effects on coronary flow were noted on the isolated sensitized heart, but an amount of the drug about fifty times that required in the histamine experiment was necessary to produce such an effect. The increased cardiac rate and amplitude of the heartbeat due to histamine or antigen reaction were not prevented by this drug. The authors note further that not all of the manifestations of shock could be prevented in the intact guinea pig by the administration of 1571F.

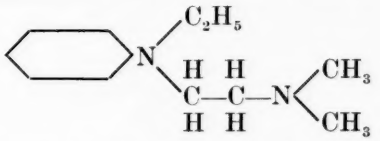
The effect of compounds 929F and 1571F on the histamine stimulation of gastric secretion was studied by Bourque and Loew.[29] They found that 1571F reduced gastric secretion in dogs with gastric pouches, but the reduction was nearly identical after pilocarpine stimulation. The gastric secretion of the dogs stimulated with food was not inhibited by 1571F. From these findings they concluded that "the data do not support the belief that 1571F is a specific antagonist to histamine." These workers found further that compound 929F

failed to modify the secretion from gastric pouches in dogs injected with pilocarpine. Hallenbeck[30] obtained results somewhat at variance with the above. He found that 1571F inhibited gastric secretory response to meat ingestion and that 929F did not inhibit secretory response to histamine or mecholyl chloride, but inhibited the response to meat ingestion.

Compounds 929F and 1571F were tried therapeutically in allergic conditions, but the toxicity of these drugs was too great and their use was promptly abandoned.

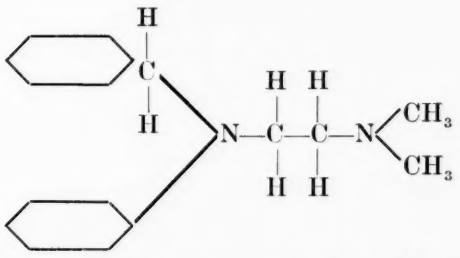
MOSNIER COMPOUNDS

In 1942, Halpern and others began to describe their results with a new series of related compounds.* Two of these compounds in particular were selected for more extended experimental and clinical studies. These were:



2325 RP

N′phenyl-N′ethyl-N-dimethylethylenediamine
(dimethylaminoethylethylaniline)



2339 RP

N′phenyl-N′benzyl-N-dimethylethylenediamine
(dimethylaminoethylbenzylaniline)

A glance at these structural formulas will indicate the similarity between these and the Fourneau compounds described earlier. Compound 2325 RP differs from 1571F only in the substitution of a dimethyl for a diethyl group. Compound 2339 RP differs from 2325 RP in the substitution of a benzyl for an ethyl group.

Halpern[31] studied the effects of these drugs on histamine and other smooth muscle excitants and on anaphylactic phenomena. The histamine contraction of the guinea pig's intestinal strip was inhibited by the addition of small amounts of these substances. The comparative indices of such activities were as follows: 1571F, 0.1; 2325 RP, 1.0; and 2339 RP, 15. In comparing the inhibiting action of these compounds on the histamine, acetylcholine, and barium chloride contraction of the intestinal strip, he found them to be much more specific against histamine. While propivane (a-phenyl valerate of diethyl-

*These compounds were prepared by M. Mosnier in the chemical laboratories of the Society of Chemical Manufacturing, Rhone-Poulenc.

aminoethanol) was twenty times more effective than 2339 RP in preventing acetylcholine contraction and about twice as effective in barium chloride contraction, 2339 RP was 1,000 times more effective than propivane against histamine contraction.

Index of efficiency in preventing intestinal contraction of guinea pig:

	Contraction due to		
	Acetylcholine	Barium chloride	Histamine
Propivane	20	2	1
2339 RP	1		1,000

Halpern produced bronchospasm in man and in guinea pigs by the inhalation of aerosoled histamine. The asthma in the guinea pigs could be prevented by the previous administration of 2339 RP, 1 mg. per kilogram hypodermically. The effect lasted two to five hours. Compounds 2339 RP was more effective in this activity than compound 2325 RP and considerably more effective than 1571F, atropine or ephedrine. It was less active than epinephrine. However, the toxicity of the latter exceeded its augmented activity.

TABLE I. AEROSOLED HISTAMINE IN GUINEA PIGS

	DOSE IN MG./KG. TO PROTECT AGAINST ASTHMA	ACTIVITY INDEX	HYPODERMIC DOSE IN MG./KG. GIVING 50-LD
1571F	20	0.25	750
2325 RP	5	1	500
2339 RP	1	5	175
Atropine	25	0.2	250
Ephedrine	> 50	> 0.1	300
Epinephrine	0.2	20	7

Although aminophylline and other xanthines are fairly effective in histamine and anaphylactic bronchospasm,[40] their efficacy is not as great as these new antihistiminic drugs nor is their action probably similar. Compound 2339 RP was also very effective in preventing shock and death in guinea pigs and dogs from histamine given intravenously. Anaphylaxis in vitro (Schultz-Dale) could also be prevented by the addition of the drug to the bath or by the previous administration to the live animal.

The pharmacologic and toxic action of the drug (particularly 2339 RP) was studied by Halpern. In guinea pigs the 50-LD was 175 mg. per kilogram, when given hypodermically, or 300 mg. when given orally. Sublethal doses caused psychomotor excitation, hallucination, jerking of muscles, polypnea, and convulsions. In prolonged experiments on dogs, 50 mg. per kilogram daily was well tolerated. Other pharmacologic actions noted were splanchnic vasoconstriction with peripheral vasodilatation, absence of modification of the effects of epinephrine or acetylcholine, a marked local anesthetic action, and temporary inhibition of renal secretion.

Halpern does not think that the drug prevents the liberation of histamine or that it increases its destruction. He postulates that this compound modifies the reaction of the organs in such a way that histamine is incapable of exercising its customary effects. He concludes that the parallelism between the pharmaco-

dynamics of the antihistaminic and antiallergic effects constitutes a direct proof for the intervention of histamine in the mechanism of allergic accidents.

Clinical Reports on 2339 RP.—Almost simultaneously with the experimental reports of Halpern there followed a series of clinical papers in the French literature on the therapeutic effects of 2339 RP, which was trade-marked "Antergan" by the manufacturers. Gaté and her associates[32] administered this drug in several types of allergic or cutaneous manifestations, with the following results: In 11 cases of urticaria, three showed remittance and five improved; in 14 cases of eczema, nine showed good results and three partial; in cases of acute eczema results were certain; in four cases of asthma, three showed remittance and two showed good results; in eight cases of hay fever and hyperesthetic rhinitis two showed remittance and two partial improvement; in four cases of migraine three showed excellent results and one partial; in two cases of dermatitis medicamentosa both were helped; in one case of anal and one case of vulvar pruritus both were helped; and in two cases of Duhring-Brocq both were helped. The daily dose of the drug was 300 to 1,000 milligrams. In 3-year-old children the dose was about one-half the adult doses. The drug was given every two hours. Intolerance effects occurred at times with the larger doses. The untoward effects were any of the following: nausea, headaches and light vertigo, burning in the stomach, but rarely vomiting. The gastric symptoms could be ameliorated by taking the medication with sugar or sodium bicarbonate. The drug was eliminated rapidly and could not be found in the urine twenty-four to forty-eight hours after administration.

The experiences of Sciclounoff and Junet[33] were similar to those of the previous authors. They particularly emphasized the good results in hay fever. The congestion of the nose and eyes was rapidly relieved and the secretions became normal; the effect lasted three to six hours. In four cases of asthma the results were partial and variable. The authors also made some experiments noting the effect of "Antergan" on the histamine skin response in man. A dose of the drug was followed in normal cases by an intradermal injection of 0.2 c.c. (concentration not stated) of histamine, with resultant diminished local action in some instances. They noted further that the histamine stimulation of gastric secretion of hydrochloric acid was not antagonized by this drug.

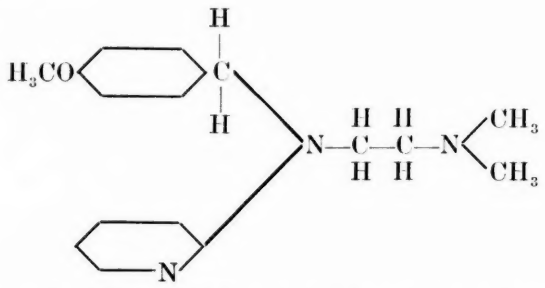
Aubertin[34] also reported favorably on the effectiveness of "Antergan" in serum sickness, alimentary urticaria, angioneurotic edema, and certain varieties of asthma. The daily doses required varied from 200 to 1,500 milligrams. The medication was tolerated better when given three-quarters of an hour to two hours after meals or with sugar or sodium bicarbonate. The untoward results mentioned are dizziness, nausea, pyrosis, and sometimes vomiting. There was a slight hypnotic effect and some diminution of appetite.

Good results were obtained by Decourt[35] with this drug in hay fever, asthma, migraine, and other allergic conditions. In a subsequent report on asthma this author[36] states that the drug is more effective as a preventive than as an active palliative remedy. He found it difficult to influence the asthma at the height of the attack. Celice and his co-workers[37] obained good results in serum sick-

ness, urticaria, and asthma. Parrot[38] obtained good results in two cases of urticaria and one case of serum sickness and found the drug effective in a variety of types of pruritus (vulvae, ani, urticaria, serum sickness, eczema). The daily doses were from 400 to 800 milligrams. The first effects of a single dose began in about fifteen minutes and lasted two or three hours. The medication was not found to be cumulative.

Parrot[39] also studied the effect of this drug on whealing phenomena in man. Drops of histamine hydrochloride 1 to 100,000 were placed on the skin and a puncture was made in each drop with a fine needle twenty minutes after the ingestion of 200 to 400 mg. of 2339 RP. The wheal and erythema failed to appear. The local reactions from the venom of Viper *Duboia* 5×10^5 were also prevented by the prior administration of the antihistaminic drug. The oral administration of this compound prevented the dermographic whealing in four out of six cases of urticaria factitia.

More recently, Bovet and his associates[39a] reported experimental findings with a new derivative:



2786 RP

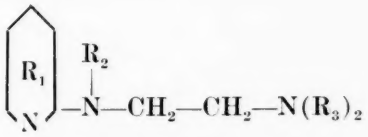
N-p-methoxybenzyl-N-dimethylaminoethyl a aminopyridine
(Neoantergan)

This compound is claimed to be more effective than antergan (2339 RP). A subcutaneous dose of 0.1 mg. per kilogram in the guinea pig prevented death from injection of five to ten lethal doses of histamine given intravenously. A dose of 1 mg. per kilogram protected against 75 lethal doses of histamine. Concentrations of 1 to 10 million and 1 to 100 million of the drug caused regression of contraction of intestinal strip produced by histamine 1 to 10 million. With the aid of trypan blue, Bonvallet and Decourt[39b] demonstrated a marked attenuating effect of this drug on the action of histamine on the permeability of capillaries in the dog. Decourt (M. J.)[39c] reports that this drug in man is less toxic and much more active than 2339 RP. In October, 1945, at a meeting of the French Association for the Advancement of Science, Halpern mentioned experiments on a new antihistaminic substance which in guinea pigs has a potency of 8 to 10 times that of neoantergan.

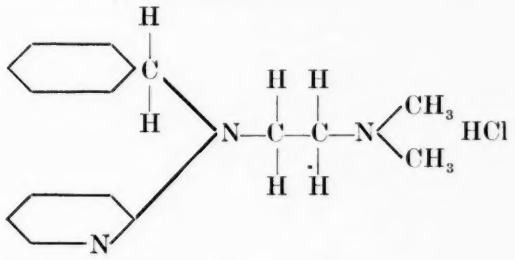
NEWEST HISTAMINE ANTAGONISTS

Pyridil-N'benzyl-N-dimethylethylenediamine.—In very recent years the search in this country for active antihistaminic compounds has been greatly

accelerated. Mayer and his associates[41] have given us a preliminary report of the action of another series of synthetic drugs, and especially of pyridine derivatives of the general formula



The most promising of this series has been found to be



63

Pyridil-N'benzyl-N-dimethylethylenediamine hydrochloride
(Pyribenzamine)

It will be apparent at a glance of the two structural formulas that Compound 63 differs only from Compound 2339 RP in the substitution of the pyridil for the phenyl ring. This slight structural alteration, however, appears to increase the antihistaminic potency of this drug. As compared with 1 mg. per kilogram of 2339 RP required for the prevention of asthma in guinea pigs from histamine inhalation, only 0.1 mg. per kilogram of Compound 63 was required. By injecting standard doses of antihistaminic drugs intravenously into guinea pigs and noting the amount of intravenous histamine to which this gives protection, Mayer obtained the following figures:

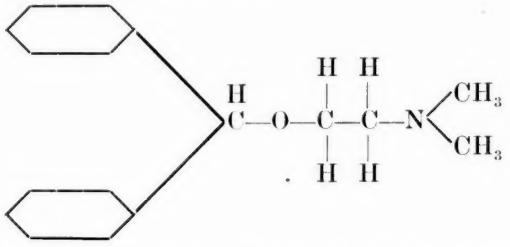
	Number of lethal doses of histamine tolerated
1571F	4- 6
2339 RP	40-60
63	100

Anaphylactic shock in guinea pigs could be prevented by the subcutaneous administration of 0.1 mg. per kilogram of Compound 63, while 1:5 mg. per kilogram of 2339 RP was required for the same effect. In a concentration of 0.02γ per milliliter, Compound 63 prevented any response of the intestinal strip to histamine diphosphate in doses from 0.2 to 1.0γ per millimeter. Its action against acetylcholine was of a much lower order.

From a personal communication from Yonkman[42] the following additional details of the action of Compound 63 are ascertained. The maximum tolerated subcutaneous dose in guinea pigs is at least 20 mg. per kilogram. The outstanding toxic symptom in animals was excitation, up to the point of convulsive seizures.

In some animals the excitation stage passed quickly into that of depression or anesthesia, which finally terminated fatally. Local tissue necrosis was present with the use of concentrated solutions hypodermically. Yonkman suggests that this drug has some features in common with local anesthetics. Further details of the pharmacology and toxicity of this drug will be reported by Yonkman, Mayer,[41] and Arbesman and his co-workers.

B-dimethylaminoethyl benzhydryl ether.—Loew and his associates[43] studied another group of synthetic compounds, mainly the benzhydryl alkamine ethers. The most promising of these compounds was



A-524

β-dimethylaminoethyl benzhydryl ether hydrochloride
(Benadryl)

Employing the method of producing fatal bronchostriction in guinea pigs by the administration of atomized histamine solution, the experimenters found[43] that it was two to four times as active as compounds 929F and 1571F. The minimum dose administered intraperitoneally which reduced the mortality rate in guinea pigs subjected to atomized histamine was one-thirtieth to one-sixtieth of LD-50 in rats or guinea pigs. The mortality and shock symptoms from intravenously administered histamine were also diminished in guinea pigs by the administration of this drug.

Further studies[44] showed that this compound was markedly effective in alleviating anaphylactic shock in guinea pigs, and was at least as active as 1571F in that capacity. Loew and his associates conclude that, "In view of the fact that these synthetic benzhydryl ethers are effective in alleviating both histamine and anaphylactic shock, the data constitute additional indirect evidence that the chief symptoms of anaphylaxis are referable to histamine."

CLINICAL ASPECTS

The clinical experiences with β-dimethylaminoethyl benzhydryl ether hydrochloride (A-524) and pyridil-N′-benzyl-N-dimethylethylenediamine hydrochloride (63) will be discussed more or less in detail in the papers that are to follow. Here we wish to point out only some of the therapeutic and experimental highlights. Our own clinical observations have been more extensive thus far with A-524 than with 63. Compound A-524 was effective in essentially all cases of urticaria factitia and dermographism[45] and was particularly helpful in the type of dermographism interfering with cutaneous testing for atopic manifestations. Our results with acute and chronic urticaria were good in a large percentage of cases, confirming an earlier report of Curtis.[46] In serum sickness and

in the itching of atopic dermatitis and other types of dermatitic itching the drug was effective. In agreement with Friedlaender,[47] we found that this drug was almost without any benefit in allergic rhinitis or asthma. This does not necessarily indicate that the mechanism of these conditions is on a different basis than the urticarias, that is, not due to histamine. It is very likely that the degree of local histamine release or response in these atopic conditions is such as not to be sufficiently influenced by the amount of the drug which can be tolerated by the subject. It was thought possible, therefore, that the topical application (nasal) in such cases might be effective. In attempting to estimate the probable concentration needed for local action it was inferred that probably the local and systemic dose relationships between vasoconstrictors might serve as a starting point. For example, the ratio between the topical nasal dose of ephedrine and its oral dose is about 1:12, the ratio between local epinephrine activity and dose by injections, about 1:25. Employing these ratios in terms of Compound 63, we find that since in the vast majority of cases of allergic rhinitis 100 mg. orally was not sufficient it would take probably at least 8 mg. or a 4 per cent solution to produce local action. Since we found that even 0.5 per cent is locally irritating, the nasal use of this drug was at least temporarily abandoned.

Some experiments of Wells and his co-workers[48] indicate that the action of this drug is to attach itself to some of the receptors on the cells which would ordinarily be occupied by histamine molecules. Apparently, no matter what the proportion of the drug to the amount of histamine, the activity of the antagonist is directed only to a portion of the histamine. Thus, it can be understood why in instances where large amounts of histamine are available the inhibition of only a portion of the latter may not be sufficient for the relief of histamine intoxication. We have additional evidence that the atopic manifestations may owe their refractoriness to this drug because of an excessive histamine release. As will be shown in another paper,[49] the topical application of A-524, as well as that of Compound 63, shows consistent and marked effect, not only on the quantitative histamine reaction, but also on the antigen-antibody response.

Our experience with Compound 63 has been limited thus far. Although this compound does not usually produce the drowsiness often associated with A-524, other types of undesirable reactions may be present. Its therapeutic effectiveness is similar to Compound 63, but we have not had sufficient observations to allow us to make a comparison between the two products.

The advent of any new drug, no matter how limited its usefulness or hazardous its use, is likely to be met by an enthusiastic army of therapists, both professional and lay. These antihistaminic drugs will constitute no exception to this rule. It is well, therefore, before we launch such remedies on the turbulent sea of overenthusiastic claims and possible regrets, to interject a few words of caution. It is particularly incumbent upon us as allergists to be conservative in our statements and cautious in our claims. We are looked upon as leaders and the pace we set will be followed or exceeded for a time. In all our therapeutic reports, let us be certain of our interpretations. Let us take into account the vicissitudes and capriciousness of behavior of allergic manifestations. Let us try to make our observations as objective as the manifestations allow.

Thus far, these drugs have been found to have only limited therapeutic use and will perhaps not be of any benefit in the majority of atopic conditions. In our clinical trials and in our reports these limitations must be repeatedly emphasized so that the indiscriminate use of these drugs will not occur. Where they are of benefit, it is important to realize that they can be expected to be palliative only, that they can only temporarily correct the result of the antigen-antibody reaction. They cannot be expected to be curative.

Finally, the toxic actions of these drugs must be anticipated. The common immediate untoward action of A-524, which consists of sleepiness and lassitude, is not serious, but does prevent the use of larger doses. There is some reason to believe that other toxic actions are possible. The most common complaints from the use of Compound 63 are gastrointestinal, although some other side effects are noted. Since these drugs are likely to be used over extended periods in individual patients, the remote toxic effects, particularly on the hematopoietic and nervous systems, should be carefully studied.

SUMMARY

1. In recent years, increased effort has been expended in the attempt to produce drugs which are antihistaminic, antianaphylactic, and antiallergic. While the first substances had a low index of efficiency and high degree of toxicity, more recent compounds have shown greater possibilities.

2. Fourneau and his followers, after trial of numerous synthetic substances, have finally settled on N-phenyl-N′benzyl-N-dimethylethylenediamine (2339 RP) as the most useful. This drug was claimed to be highly effective in allergic manifestations. In this country, the recent ventures in this field have consisted of experimentation, particularly with two compounds, β-dimethylaminoethyl benzhydryl ether (A-524) and pyridil-N′benzyl-N-dimethylethylenediamine (63).

3. Both of these drugs apparently have definite effect on some of the manifestations of allergy, such as urticaria and angioneurotic edema in a considerable percentage, and possibly on some other manifestations and pruritus.

4. Even at this early stage of experimentation it is evident that the use of these drugs will be limited because they will not be effective in many of the manifestations of allergy and because of the toxicity and undesirable reactions. Further limitation of their effectiveness is, of course, evident from the fact that, at best, such remedies are only palliative and that they do not produce any lasting benefit.

5. It is hoped that the advent of this type of therapy will not becloud the issue nor dampen the ardor of our search for information of more basic value that will help us to understand the mechanism of the allergic reaction and the constitutional background of allergy, and find a means for the correction of both.

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Special Reports

THE GENERAL ADAPTATION SYNDROME AND THE DISEASES OF ADAPTATION*

HANS SELYE, M.D., PH.D., D.SC., F.R.S.(C.)†
MONTREAL, CANADA

INTRODUCTION

TEN years have passed since the first description of the "alarm reaction," and many publications during this decade have dealt with this phenomenon and with the "general adaptation syndrome," of which it forms a part. It is becoming increasingly more obvious that certain physiologic mechanisms, in which the endocrine system plays a prominent role, help to raise resistance to damage as such, irrespective of the specific nature of the damaging agents. A number of very interesting observations were made quite recently which show that the formation of γ-globulin and of antibodies is markedly increased during the alarm reaction and the latter appears to play an important role in specific immunologic phenomena as well as in the fight of the organism against non-specific damage as such. Interest in the general adaptation syndrome received a further impetus as a result of investigations suggesting that some of the most important diseases of human pathology (such as hypertension, nephrosclerosis, and the rheumatic diseases) may represent by-products of the endocrine reactions, which are at play in the general adaptation syndrome. It was considered a timely enterprise, therefore, to survey this field now for the members of the American Academy of Allergy and thus to supply them with a guide to the rather scattered and polyglot pertinent literature. In order to familiarize himself with different points of view, the reader is also referred to several earlier reviews on the general adaptation syndrome.[10, 11, 235, 295, 358, 569, 571, 577, 629, 634, 654]

DEFINITION AND TERMINOLOGY

Before entering upon a discussion of a relatively new concept, such as that of the general adaptation syndrome, it is essential to give a clear definition of the subject and the terminology to be used. In some sciences (e.g., mathematics) definitions are unchangeable laws which make a concept what it is; in biology, however, definitions are given merely as concise descriptions of phenomena as

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†Professor and Director of the Institute of Experimental Medicine and Surgery, University of Montreal, Montreal, Canada.

they are known at the time, with the view of modifying them as soon as further observations necessitate it. It is with this in mind that the following definitions are presented.

The *general adaptation syndrome* is the sum of all nonspecific, systemic reactions of the body which ensue upon long-continued exposure to stress. It is distinct from the specific adaptive reactions, such as the development of the musculature following prolonged physical exercise, the allergic and immunologic phenomena elicited by foreign proteins or microorganisms, et cetera. These latter reactions usually endow the body with a great deal of resistance against the particular agent to which it has previously been exposed, but both the manifestations of these adaptive reactions and the resistance which they confer upon the body are specific to the agent which elicited them.

In the course of our work on the pathologic and biochemical changes elicited by various noxious agents, we were struck by the fact that certain manifestations are always the same, irrespective of the specific nature of the eliciting damaging agent. It is the sum of these nonspecific adaptive reactions that is referred to as the "general adaptation syndrome."

It has been found, furthermore, that, if an organism is continuously exposed to a certain type of stress, the resulting general adaptation syndrome evolves in three distinct stages, namely, the "alarm reaction," the "stage of resistance," and the "stage of exhaustion." Perhaps because historically the alarm reaction was the first to be described, or because of its striking name, it received the greatest attention in the literature. Indeed, some workers fail to distinguish clearly between the alarm reaction and the general adaptation syndrome as a whole. It is especially important, therefore, to emphasize that the former is merely the first stage of the latter.

The *alarm reaction* is the sum of all nonspecific systemic phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted. Some of these phenomena are merely passive and represent signs of damage or "shock"; others are signs of active defense against shock. In the case of moderately severe damage, from which recovery is possible, most of the signs of damage become evident before the signs of defense. Hence, the alarm reaction may in turn be subdivided into two more or less distinct phases: the phase of *shock* and the phase of *countershock*. If exposure to damage is not very sudden or if the damaging agent to which the organism is exposed is relatively mild, countershock phenomena may become evident without any preceding phase of actual "shock." Unfortunately, no satisfactory definition of shock has as yet been given. In most cases one or the other symptom of shock was singled out as its basic feature, and the condition was then defined as one characterized by that symptom (e.g., hypothermia, hypotension, hemoconcentration, capillary permeability, hypochloremia, acidosis, and depression of the nervous system). Such definitions are not satisfactory because under certain conditions any one of the so-called "characteristic" symptoms may be in evidence although there is no shock and, conversely, shock may develop in the absence of one or the other of these symptoms.

It seems more appropriate, therefore, to say that shock is a condition of suddenly developing, intense, systemic (general) damage. This definition, though perhaps not very instructive, is necessarily correct, since it is merely a brief outline of the essential phenomena which induced physicians to coin the term "shock." This latter term always implies a suddenly developing condition, so that damage caused by chronic ailments cannot be thus described. It also implies that the damage is systemic (or general), hence localized lesions, no matter how severe, should not be considered as shock unless they secondarily lead to generalized damage.

Shock may develop in two forms; one is almost instantaneous, the other appears only after a few hours. Some investigators, therefore, distinguish between *"primary" and "secondary" shock*. It has been asserted that such a distinction is all the more important since primary shock is due to nervous stimuli and secondary shock is due to intoxication with endogenous substances. This is not definitely proved, however, and since even nervous impulses are transmitted by humoral substances, the distinction would not be as sharp as was originally assumed, in any case. Furthermore, even in the case of exposure to damaging agents which lead to fatal shock within less than an hour, the pathologic and biochemical changes may be practically the same as those seen in secondary shock. It is questionable, therefore, whether these two types should be distinguished as essentially different or regarded as an acute and a delayed form of the same process. The recent discovery of countershock phenomena may explain cases in which a distinct period of "primary shock" was followed by "secondary shock" after an intermediate period of relative well-being. It is possible that in such cases the intermediate shock-free period is merely the equivalent of the countershock phase which later proves insufficient and gives way to fatal shock.

The term *collapse* has been used often as synonymous with primary shock, but here again there is little justification for a special name. Moon[435] summarizes as follows: "Collapse designates a sudden failure of the circulation. When this presents, as it usually does, the features embodied in the definition of shock, the terms should be regarded as interchangeable." Allen,[14] on the other hand, believes that primary and secondary shock are two entirely different conditions, mainly because the blood-count changes, characteristic of the latter, are usually not found in the former. He expressed the view that "it is questionable whether the name shock should continue to be applied to both." The initial irregularities in the blood count during the first hour of the shock phase of the alarm reaction will be discussed later; suffice it here to say that they are hardly of sufficient significance to justify the distinction between two different types of shock.

The value of the term "shock" has been greatly diminished as a result of the numerous confusing definitions with which it is associated, yet it would be difficult to eradicate it now, although terms such as *"exemia"*[87] and *"histotoxicosis"*[14] have been suggested.

More recently, the term *"crush syndrome"* has been introduced to designate a particularly delayed type of general damage which usually follows severe

crushing of extensive body regions. It is mainly characterized by renal lesions which appear several days after the eliciting trauma.[39, 84, 133a, 158, 168a, 169, 230, 440]

The *stage of resistance* represents the sum of all nonspecific systemic reactions elicited by prolonged exposure to stimuli to which the organism has acquired adaptation as a result of continuous exposure. It is characterized by an increased resistance to the particular agent to which the body is exposed and a decreased resistance to other types of stress. Thus the impression is gained that, during the stage of resistance, adaptation to one agent is acquired "at the expense of" resistance to other agents. It is also noteworthy that most morphologic and biochemical changes of the "alarm reaction" disappear during the stage of resistance and indeed in some cases the direction of the deviations from the normal is reversed (e.g., hypochloremia during the alarm reaction, hyperchloremia during the stage of resistance).

Finally, *the stage of exhaustion* represents the sum of all nonspecific systemic reactions which ultimately develop as the result of very prolonged exposure to stimuli to which adaptation had been developed but could no longer be maintained.

The characteristics of these three stages are described in the section entitled, "Course of the General Adaptation Syndrome."

By *specific resistance* we mean that type of inurement which increases resistance only against the particular type of stress to which the body had been exposed; conversely, *nonspecific resistance* designates the ability of the body to withstand stress qualitatively different from that to which it had been adapted.

The term "*adaptation energy*" is used to describe the ability of the organism to acquire resistance to stress.

In connection with the terminology of the general adaptation syndrome, it should be noted that some investigators use the term "alarm reaction" to describe certain nervous phenomena whose relationship to the general adaptation syndrome has not been fully clarified as yet.[332, 693] On the other hand, the "*anamnestic reaction*" is most probably an integral part of the general adaptation syndrome, as we shall see in another section. It has been defined as "the enhancement of antibody titer which follows the injection of a variety of nonspecific substances other than the original antigen."[155]

HISTORY OF THE GENERAL ADAPTATION SYNDROME

It is rather instructive to survey the historic development of the alarm reaction concept. The fact that such a common biologic phenomenon as the alarm reaction was not discovered long ago probably finds its explanation in that previous investigators studied only certain aspects of this problem and failed to recognize that they were dealing with a general reaction in which the object of their particular attention was merely one of a set of correlated symptoms. The most ancient observations along these lines are those on *traumatic shock*, which is now recognized as fundamentally related to toxic, spinal, burn, x-ray, and other types of shock; all conditions representing the first phase of the alarm reaction.

In 1911, Bianchi[56, 57] made an observation which may have been the first evidence of the existence of a countershock phenomenon. He noted that rabbits receiving intravenous injections of toxic tissue extracts become more resistant to subsequent injections either of the same or of different organ extracts. This phenomenon was studied also by Champy and Gley,[98, 99] who gave it the name "*tachyphylaxis.*" Numerous investigators confirmed and extended these observations.[190, 467, 501] Almost at the same time, Ancel and his co-workers[24, 344] described similar observations under the name of "*skeptophylaxis.*" Both these terms were chosen to imply a rapid defense reaction; tachyphylaxis meaning quick readiness and skeptophylaxis meaning lightning readiness.

Tzanck and collaborators[3, 643-646] introduced the term "*biophylaxis*" to designate all nonspecific defense mechanisms (phagocytosis, inflammation, etc.), exclusive of true immune reactions. These authors limited themselves largely to theoretical considerations and gave so little factual evidence that it is almost impossible to determine exactly what phenomena they observed. It appears, however, that their concept came very close to what Cannon[89, 90] termed "*homeostasis.*" Lassablière[354] found that injection of such "nutrients" as 40 per cent glucose, rice water, wine, beer, organ extracts, milk, etc. increases the resistance of mice to cobra venom, a phenomenon which he described as "*trophophylaxis.*"

In 1913, the Belgian histologist Dustin[160, 161] began a series of studies on the effect of certain drugs on nuclear pyknosis and mitotic division. He concluded that certain drugs, which he termed "poisons caryoclasiques," increase the number of pyknoses, especially in the thymus and lymph glands, and decrease the number of mitotic figures. He and his followers designate this response "*crise caryoclasique.*"[73, 95, 104, 140, 160a, 162, 242, 243] Later, however, regeneration with an increase in the number of mitoses occurs. More recently, it was concluded that some of these drugs act more specifically on pyknosis, others on mitosis. It is well to keep in mind that all so-called "caryoclastic drugs" which the writer had occasion to examine produced typical signs of the alarm reaction. This has been demonstrated especially clearly[360] for colchicine—one of the most active drugs of this series. It was noted, furthermore, that waves of pyknosis in the thymus and lymph nodes are produced by all alarming stimuli. This is true not only of drugs but also of spinal and surgical shock, muscular exercise, exposure to cold, etc., so that it appears rather likely that Dustin and his school were studying one phase of the alarm reaction rather than the specific pharmacologic action of a special class of drugs.

In 1921, the French physician Widal and his school[684] gave a detailed description of a clinical syndrome which they termed "*crise hémoclasique.*" This was first observed in cases of cold hemoglobinuria and later in many other clinical conditions, such as acute infectious diseases and allergic reactions. The outstanding features of this syndrome are leucopenia, decrease in the refractive index of the serum, and decrease in blood clotting time and in blood pressure. Albuminuria and fever are sometimes also observed, but these are inconstant. Both Widal's reaction and the alarm reaction represent responses to acute, critical situations, and it seems likely that there is a close relationship between

them. Since the symptoms of the alarm reaction, however, have not as yet been studied sufficiently in man, it is impossible to say whether the two syndromes are actually identical.[140a]

The fact that the alarm reaction confers a certain degree of nonspecific resistance upon the organism makes it probable that it is also closely related to the so-called "*nonspecific therapy*" about which much has been written, but unfortunately, little is known as yet. The relevant literature has repeatedly been reviewed.[272, 668-670] It is claimed that administration of certain nonspecific damaging substances leads to the production of "metabolites" which increase the resistance of the organism against various diseases ("*Leistungssteigerung und Protoplasmaaktivierung*"). It is probable that these phenomena are closely related to the increase in resistance seen during the afore-mentioned "phylactic" reactions and during the countershock phase of the alarm reaction.

The "*syndrome polypeptidotoxique*"[372] which develops in acute hepatic insufficiency after burns or trauma and is characterized by an unusually high polypeptide concentration in the blood, evidently also belongs to this group. The extensive protein breakdown characteristic of the shock phase of the alarm reaction is probably the cause of the increase in polypeptides.

Rössle[514-517] was the first to formulate the concept of "*serous inflammation*" (*seröse Entzündung*), which was later elaborated by Eppinger[176] and his school. It is based on the observation that under the influence of various noxious agents the normally low protein concentration of the intercellular fluid rises as a result of migration of plasma into the intercellular spaces. This migration—which is referred to by Eppinger as "albuminuria into the tissues"—is the result of increased capillary permeability. It is accompanied by an increase in the sodium, chlorine, and water content and a decrease in the potassium phosphate content of the tissues. It has been noted[395] that lesions in the intestinal tract, such as are seen in the alarm reaction, may accompany this syndrome in man, an observation which emphasizes the similarity between these two conditions.

The "*Maladie-post-opératoire*" of Leriche, which has attracted much attention,[346, 347] is likewise essentially identical with the shock phase.

The *alarm reaction,* as a clearly defined separate entity, was first described in 1936,[540] when it was realized that, in response to a great variety of agents, the organism responds with the same set of symptoms, which—it was concluded—represent "a call to arms" of the body's defense forces. Subsequent work showed that the reaction consists of two more or less distinct phases. The transition between these is not always sharp and some of their manifestations may overlap, but, generally speaking, it may be said that the following are characteristic of the first or *shock phase:* tachycardia, decrease in muscular tone and body temperature, formation of gastric and intestinal ulcers, hemoconcentration, anuria, edema formation, decrease in blood chlorides, acidosis, a transitory rise followed by a decrease in blood sugar, leucopenia followed by leucocytosis, and discharge of adrenalin from the adrenal medulla. This phase may last anywhere from a few minutes to twenty-four hours, depending on the intensity of the damage inflicted, but, unless the termination is fatal, it is always followed

by the *countershock phase*. The latter is characterized by: an enlargement of the adrenal cortex whose cells show signs of increased activity, acute involution of the thymus and other lymphatic organs, and a reversal of most signs characteristic of the shock phase. Thus, there is blood dilution and increase in blood volume, increase in blood sugar and blood chlorides, alkalosis, diuresis, and often a rise in body temperature.

If treatment with the alarming stimulus is continued, the countershock phase gradually merges into the *stage of resistance*, during which most of the morphologic lesions regress and specific resistance (to the eliciting stimulus) reaches its peak.

Finally, it was found that even a perfectly adapted organism cannot indefinitely maintain itself in the stage of resistance. If exposure to abnormal conditions continues, adaptation wears out, the lesions characteristic of the alarm reaction (involution of lymphatic structures, adrenal enlargement, gastrointestinal ulcers) reappear, and the *stage of exhaustion* develops during which further resistance becomes impossible.[312, 542, 543, 557, 577] These observations, which will be described in detail later (see section on "Course of the General Adaptation Syndrome"), led to the conception that any nonspecific noxious agent which causes sudden general, systemic damage elicits the shock phase of the alarm reaction, probably because it liberates toxic metabolites from the tissues. The theory was proposed that, if the damage is not too severe and hence permits survival, the damaging agent (perhaps through a hypothetical toxic metabolite produced under its influence) acts on the anterior lobe of the pituitary and stimulates it to discharge adrenotropic hormone. This in turn stimulates the adrenal cortex to produce an excess of corticoid hormones, which help to raise the resistance of the body and elicit the characteristic countershock phenomena (e.g., involution of the lymphatic organs). All essential tenets of this theory have since been confirmed by a variety of experimental techniques, and this original interpretation still represents the most commonly accepted view.

However, except for the interpretation of "shock," the clinical importance of the general adaptation syndrome did not become evident until quite recently when it was shown that, under special experimental conditions, exposure to nonspecific damaging agents (e.g., cold) causes hypertension and nephrosclerosis in animals.[574] This hypertension and nephrosclerosis were found to be accompanied by an enlargement of the adrenal cortex and the question arose whether the increased production of corticotropic hormones during the general adaptation syndrome could be the pathogenic agent involved. Further experiments showed that pure synthetic desoxycorticosterone acetate,[592, 605] as well as anterior pituitary extracts,[576] is particularly active in eliciting nephrosclerosis and hypertension in animals; these changes are not infrequently accompanied by myocardial lesions and arthritides, similar to those seen in patients with rheumatic fever. As we shall see later, there is still some doubt concerning the intimate mechanism through which nonspecific damaging agents and hormonal preparations cause the afore-mentioned experimental diseases. The fact remains, however, that all experimental observations are most readily compatible with the view that, during the general adaptation syndrome, certain hormones of

the anterior pituitary and adrenal cortex are produced in excessive amounts in order to increase resistance; this defensive endocrine response is valuable inasmuch as it facilitates adaptation to stress (e.g., infections, intoxications, nervous commotions, and cold), but the resulting endogenous hormone overdosage may become the cause of certain cardiovascular, renal, and joint diseases. Thus developed the concept that many of the most common maladies of man are "*diseases of adaptation,*" that is to say, the by-products of abnormal adaptive reactions to stress.[577]

THE ALARMING STIMULI

By definition, any agent capable of producing an alarm reaction is an "alarming stimulus." It is well to realize, however, that agents causing merely local damage, which requires no general adaptive adjustment (e.g., amputation of limbs), are relatively mild alarming stimuli, while exposure to even moderate cold, solar or roentgen radiation, muscular exercise, etc., which evoke intense adaptive responses, produces very severe alarm reaction symptoms. It should be emphasized, furthermore, that the alarm reaction is not necessarily a pathologic phenomenon. In the case of mild alarm reactions there is no "shock" in the ordinary sense of the word. Slight hyperglycemia, tachycardia, and leucocytosis may be the only detectable symptoms and there is a continuous series of transitional steps between the definitely physiologic adaptive processes to the stress and strain of everyday life and the most severe alarm reactions which cause death during the "shock phase."

The systemic effects caused by exposure to a variety of alarming stimuli have frequently been reviewed. Perusal of the relevant publications reemphasizes the great similarity between the response of the organism to such a variety of alarming stimuli as: *traumatic shock,*[52, 87, 339, 347, 435, 536 542, 545] *obstetric shock,*[412, 521, 607, 617, 618] *"gravity shock,"*[112] *muscular exercise,*[502, 545, 563, 621] *infectious diseases,*[304, 502] *hemorrhage,*[191] *nervous shock,*[304, 545] *exposure to cold,*[488, 502, 608] *temporary blood vessel occlusion,*[13, 14, 290-292, 687] *reduced oxygen tension,*[146, 231, 629] *burns,*[177, 195b, 273] *drugs,*[138, 401, 502, 545] *bacterial toxins,*[464] *x-rays* or *radium rays,*[173, 361, 438, 439, 493, 494, 502, 537] and *solar rays.*[480]

A few alarming stimuli deserve special consideration. Thus, it is noteworthy that *colchicine,* a typical caryoclastic drug, is, according to Leblond and Segal,[360] the most active alarming stimulus yet described. It is also of interest that, if given in sufficiently high doses, natural and synthetic *folliculoids* ("estrogens") are capable of producing an alarm reaction.[473, 566, 596] As will be seen later, *muscular exercise* differs from all other known alarming stimuli in that it causes remarkably little shock and very pronounced countershock phenomena. It has been claimed that, in contradistinction to traumatic shock, the blood concentration diminishes in *spinal shock.*[443] Henderson[265] remarked that "the only significance which the latter observation bears for the problem of traumatic shock is the additional evidence which it affords that traumatic and spinal shock are two totally distinct conditions." These conclusions were later disproved, since it was found that spinal shock produces all the characteristic signs of the shock phase, including hemoconcentration; the blood dilu-

tion referred to previously appears only during the countershock phase, so that spinal shock may be regarded also as an alarming stimulus.[539] Purely *functional nervous commotions* (rage, fear) may act as strong alarming stimuli,[542] but, since the same is true of deep anesthesia, there is no reason to assume that the functional integrity of the nervous system is essential for the development of the alarm reaction.[569] Even *fasting* must be regarded as a typical, though rather slowly acting, alarming stimulus, since it elicits such characteristic symptoms as adrenal enlargement, thymus atrophy, hypochloremia, hypoglycemia followed by hyperglycemia, hemoconcentration, and gastrointestinal erosions.[567]

After what has been said, it is hardly necessary to insist further upon the nonspecific nature of the alarm reaction. It is noteworthy, however, that many lesions which had previously been thought to be due to the specific action of certain stimuli, have now been recognized as manifestations of the resulting alarm reaction. To give but a few characteristic examples, many of the changes produced by *x-rays,*[362] *protamine,*[655] the so-called "critical period" following *parabiosis,*[120] *fever* caused by ultrahigh-frequency radio emanations,[50] *anoxia,*[146, 351, 355] *spinal cord transection,*[207] the injection of *"menstrual toxin,"*[614] and *burns*[232] are no longer considered to be specific lesions but are now interpreted as manifestations of alarm reactions produced by these damaging agents.

Finally, it should be kept in mind that any alarming stimulus—if it is given in a dosage compatible with the maintenance of life and for a sufficiently prolonged period—is capable of eliciting the other two stages of the adaptation syndrome as well. In this connection it is interesting that a certain degree of adaptation can be acquired even to the shock-producing action of mechanical trauma.[458, 639]

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(*To be continued.*)

Editorial

Certification in Allergy

In reply to many inquiries, the American Academy of Allergy desires to clarify the problem of certification in Allergy. At present, recognized certification in Allergy requires prior certification in Internal Medicine or in Pediatrics, followed by examination and certification in Allergy. Neither the American Board of Dermatology nor the American Board of Otorhinolaryngology has indicated its desire or willingness to certify in Allergy.

Wide publicity has been given recently to certification in Allergy by a self-constituted group which calls itself the American Board for the Certification of Allergists. This so-called board has no connection with the Advisory Board of Medical Specialties or with any of its constituent specialty boards sponsored by the American Medical Association. The American Board for the Certification of Allergists has failed to follow the established procedure of filing an application with or obtaining approval of the Advisory Board for Medical Specialties or of the Council on Medical Education and Hospitals of the American Medical Association. It is clear, therefore, that the American Board for the Certification of Allergists is not to be confused with the established certifying boards; neither will it replace, or act for or instead of, any of the established certifying boards. Furthermore so-called certification by this unofficial group will not be recognized by the Advisory Board for Medical Specialties or by any of its constituent boards, the Council on Medical Education of the American Medical Association, the American Medical Association, Hospitals, or medical schools. Under the circumstances, neither the Directory of Medical Specialists nor the Directory of the American Medical Association will include such certification.

EXECUTIVE COMMITTEE
AMERICAN ACADEMY OF ALLERGY

American Academy of Allergy

NEWS AND NOTES

Orientation Course in Clinical Allergy

Marquette University School of Medicine offers an orientation course in clinical allergy under the sponsorship of the American Academy of Allergy. The course will last five days, Oct. 7 to 11, 1946, inclusive, and will be held at the Medical School, Milwaukee, Wis. The registration fee is $40.00 (no registration fee for residents or interns).

This course is planned to acquaint physicians with basic principles of diagnosis and management of allergic diseases.

FACULTY

Harry Beckman, M.D., Professor of Pharmacology, Marquette University School of Medicine, Milwaukee, Wis.

Theodore B. Bernstein, M.D., Instructor in Medicine, Northwestern University Medical School, Evanston, Ill.

Milton Cohen, M.D., F.A.C.P., Associate Editor, The Journal of Allergy, Cleveland, Ohio.

Robert A. Cooke, M.D., F.A.C.P., Attending Physician and Director, Department of Allergy, Roosevelt Hospital, New York, N. Y.

Leo H. Criep, M.D., Assistant Professor of Medicine and Lecturer in Immunology, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

O. C. Durham, Chief Botanist, Abbott Laboratories, Chicago, Ill.

Charles H. Eyermann, M.D., Past President, American Association for the Study of Allergy, St. Louis, Mo.

Samuel M. Feinberg, M.D., F.A.C.P., Associate Professor of Medicine, Chief of Division of Allergy, Northwestern University Medical School, Chicago, Ill.

Harry R. Foerster, M.D., Assistant Professor of Dermatology, University of Wisconsin Medical School; and Associate Clinical Professor of Dermatology, Marquette University School of Medicine, Milwaukee, Wis.

Harry L. Huber, M.D., F.A.C.P., Past President, Society for Study of Asthma and Allied Conditions; and Past President, American Association for the Study of Allergy. Former Associate Professor of Medicine, University of Chicago.

Ben Z. Rappaport, M.D., Associate Professor of Medicine and Director of Clinical Investigation of the Allergy Unit, University of Illinois, Chicago, Ill.

A. B. Schwartz, M.D., Associate Clinical Professor of Pediatrics, Marquette University School of Medicine, Milwaukee, Wis.

John M. Sheldon, M.D., Associate Professor of Medicine, University of Michigan Medical School, Ann Arbor, Mich.

Theodore L. Squier, M.D., F.A.C.P., Associate Clinical Professor of Medicine, Marquette University School of Medicine, Milwaukee, Wis.

Oscar Swineford, Jr., M.D., F.A.C.P., Professor in Practice of Medicine, University of Virginia Medical School, Charlottesville, Va.

Inquiries should be addressed to Eben J. Carey, M.D., Dean Marquette University School of Medicine, Milwaukee 3, Wis.

PROGRAM

Monday, October 7

9:00-9:30 Registration

9:30- 9:45 Welcome, Dr. Eben J. Carey, Dean Marquette University School of Medicine
9:45-10:00 "The Development of Allergy," Dr. Theodore L. Squier
10:00-12:30 "The Basic Immunology and Physiology of Allergy," Dr. Milton B. Cohen
1:30- 3:00 "Diagnosis of Allergic Disease—History, Skin Testing: Methods, Limitations, and Abuse," Dr. Ben Z. Rappaport
3:00- 5:00 "Seasonal Hay Fever," Dr. Milton B. Cohen
5:00- 5:30 "Systemic Reactions: Recognition, Prevention, and Treatment," Dr. Ben Z. Rappaport

Tuesday, October 8

9:00-11:00 "Aerobiology. Evaluation of Air-Borne Allergens," Mr. O. C. Durham
11:00-12:30 "Food Allergy and Gastrointestinal Allergy," Dr. Ben Z. Rappaport
1:30- 3:30 "Fungus Allergy," Dr. Samuel M. Feinberg
3:30- 4:30 "Drug and Serum Allergy," Dr. Theodore B. Bernstein
4:30- 5:30 "Urticaria and Angio-edema," Dr. John M. Sheldon
8:30-10:00 Round-table Discussion—"Hay Fever," Drs. Cohen, Feinberg, Rappaport, and Sheldon

Wednesday, October 9

9:00-10:30 "Pediatric Allergy and Infantile Eczema," Dr. A. B. Schwartz
10:30-11:30 "Contact and Occupational Dermatoses," Dr. Harry R. Foerster
11:30-12:30 "Atopic Dermatitis," Dr. John M. Sheldon
1:30- 3:00 "Pharmacology of Drugs Used in the Treatment of Allergic Disease," Dr. Harry Beckman
3:00- 4:30 "Allergy to Biologicals: Liver, Insulin, etc.," Dr. Samuel M. Feinberg
4:30- 5:30 "Hematologic Allergy," Dr. Theodore L. Squier

Thursday, October 10

9:00-10:00 "Perennial Rhinitis," Dr. Leo H. Criep
10:00-12:30 "Migraine and Allergic Headache," Dr. Charles H. Eyermann
1:30- 2:30 "Physical Allergy," Dr. Oscar Swineford
2:30- 4:00 "Recapitulation of Non-specific Therapy in Allergic Disease," Dr. Leo H. Criep
4:00- 5:30 "Asthma—Classification and Diagnosis," Dr. Oscar Swineford
8:30-10:00 Round-table Discussion—"Allergic Therapy," Drs. Beckman, Eyermann, and Swineford

Friday, October 11

9:00-11:00 "Asthma—Pathology and Management," Dr. Harry L. Huber
11:00-12:30 "Status Asthmaticus," Dr. Charles H. Eyermann
1:30- 2:30 "Cardiac Asthma," Dr. Oscar Swineford
2:30- 4:30 "Bacterial Allergy," Dr. Robert A. Cooke
8:30-10:00 "Allergy in Relation to Internal Medicine," Dr. Robert A. Cooke

Statement of Activities

MEMBERSHIP

Members.—Any physician interested in Allergy may, on recommendation of the Executive Committee, be elected to membership.

Fellows.—On attainment of certain qualifications, members may be elevated to Fellowship.

ACTIVITIES

Annual Scientific Meeting.—This is held in various cities for the purpose of presentation and discussion of papers on fundamental research in Allergy and on significant clinical studies. Guest lecturers, authorities in their fields, from allied sciences are invited. Commercial exhibits of interest to allergists are held.

THE JOURNAL OF ALLERGY.—This is the official publication of the Academy and is the repository for papers dealing with research in fundamental problems in clinical and laboratory fields. Abstracts of current Allergy literature and Academy news appear regularly.

Education.—

A. Undergraduate: This comprises a study of medical school curricula and aids in establishing at least minimal satisfactory courses in Allergy.

B. Graduate: Fellowships and residences for physicians who desire to specialize in Allergy are assembled. (Available and approved residences are on file with Dr. R. A. Cooke, 60 East 58th Street, New York City.)

C. Postgraduate: Basic and advanced courses in cooperation with medical schools in several cities are given each year.

New Drugs and Appliances.—The Committee on Pharmaceuticals and Medicaments is available to cooperate with commercial drug manufacturers and the Foods and Drugs Administration to evaluate new remedies.

Pollen Survey Committee.—This Committee is engaged in procurement and dissemination of information on pollen allergens. It has made much progress in standardization of techniques employed in pollen counting, which may serve as a basis for similar studies with other types of allergens.

Certification in Allergy.—Through its Advisory Board, the Academy works with the official certifying bodies of the American Board of Internal Medicine and the American Board of Pediatrics.

IN MEMORIAM

ARTHUR BEATTYS BERRESFORD

(1903-1946)

ARTHUR BEATTYS BERRESFORD of Ithaca, New York, died on April 16, 1946, at the Post Graduate Hospital, New York City, after a long illness. Born in Milwaukee forty-two years ago, he was the son of the late Arthur William Berresford, noted electrical engineer, who was once President of the American Institute of Engineers, and the late Mrs. Florence King Berresford.

Dr. Berresford received an Electrical Engineering degree from Cornell University in 1929 and a Bachelor of Arts degree from that University in 1931. In 1935, he received his Doctor of Medicine degree from Boston University School of Medicine. After serving his internship at the Waterbury (Conn.) Hospital, he practiced medicine in Ithaca, New York. In 1942-1944 he was research fellow in the Department of Allergy, Roosevelt Hospital, New York City. He was on the staff of the Tompkins County Memorial Hospital, Ithaca, and the Cornell University Infirmary.

Dr. Berresford was coauthor of *Know Your Hay Fever* and several scientific articles on allergy. He was a member of the American Academy of Allergy,

American Medical Association, New York State Medical Society, the Collectors Club, and the New York Athletic Club.

He leaves a widow, Mrs. Katherine Kennan Berresford, a daughter, Miss Barbara Kennan Berresford, and a brother, John King Berresford of Durham Center, Conn.

Dr. Berresford's death is a very real loss to the medical profession. It will be particularly felt in the field of Allergy to which he had devoted himself. He was an indefatigable worker and combined a great human interest in his patients and the relief of their distress and suffering with a keen desire for the investigation of untrodden and unknown fields. To this was added a whimsical humor and charming manner which smoothed the way for many a chronic sufferer who needed sympathy as well as medical attention.

He utilized his previous training as an engineer in many ways, one example of which was in the development of a very efficient pollen dehydrator while working in the Allergy Clinic at Roosevelt Hospital. His article on the "Musings of an Engineer Doctor" read before the American Institute of Electrical Engineers was a delightful blending of common sense and subtile humor poking fun at the foibles of both engineers and doctors. In his "Chapters on Clinical Applications" in the book *Know Your Hay Fever,* he was most successful in translating medical terms and procedures into language understandable to the laity. Just before his death, he finished a book on asthma giving many new and original personal viewpoints, interesting and well worth considering. It is to be hoped that this book will be published in spite of the fact that he is no longer here personally to supervise its final production.

It is hard to realize that a man of such promise, just entering on the most productive time of his career, has been called away, and those of us who were privileged to know him intimately will greatly miss his helpfulness, cooperation, and cheery smile.

(Signed)
ALBERT VANDER VEER
ROBERT A. COOKE

WILLIAM WADDELL DUKE

(1883-1946)

ON APRIL 20, 1946, the Obituary Column of *The Journal of The American Medical Association* stated: "William Waddell Duke, distinguished internist, died at his home in Kansas City, Missouri, aged 62." The announcement reviews his life and his distinguished career. Here indeed was a giant among men.

His grandfather founded the pony express, and his father contributed significantly to the development of the west. For "Billy" Duke there were no longer interesting physical frontiers. His early contact with Lafayete B. Mendel stimulated him to turn his talent to the scientific frontiers of medicine. His earlier work dealt with anemia, blood transfusion, and hemorrhagic dis-

eases. Chapter 6 in his book, *Oral Sepsis in Its Relationship to Systemic Disease,* written in 1918, is entitled "Toxic Effects of Oral Sepsis." Here, in his first discussion of Allergy, he demonstrated the extent of his fundamental knowledge and his breadth of view.

By 1925, he had published his clinical experiences in a volume entitled *Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy.* In addition to a very complete discussion of the clinical aspects of these conditions, he added his observations on cases of reaction to heat, cold, light, and other physical agents. In this work, he alluded to most of the established advances in Allergy that have since been made.

During his active career his friendliness and enthusiasm stimulated his contemporaries and influenced their professional growth and development.

His death deprives the younger generation of contact with one of the true pioneers in Allergy.

(Signed)
MILTON B. COHEN

Book Reviews

Cosmetics and Dermatitis. Louis Schwartz, M.D., and Samuel M. Peck, M.D., New York, 1946, Paul B. Hoeber, Inc., pp. 187, illustrated.

These two distinguished authorities on cosmetic dermatitis, aware of the high incidence of this disorder, realized the lack of systematic knowledge of cosmetics and their effects on the skin. Their studies are the subject of this book. The presentation is made in an orderly manner, beginning with the anatomy and physiology of the skin. Creams, hair preparations, perfumes, etc., are described; the surprising number of chemical ingredients that go into their manufacture are listed; and their role as contactants is emphasized. Lesions are well illustrated, and bibliographies are given. Final chapters deal with diagnosis, methods of testing new cosmetics, and treatment.

The subject matter is so concisely and clearly presented that although the book is a small one, it contains a wealth of material. It is a welcome addition to the literature of dermatologic allergy.